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THE OCCURRENCE AND SIGNIFICANCE OF MYOCARDIAL FAILURE IN ACUTE HEMORRHAGIC NEPHRITIS

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Submitted for publication October 31, 1938

It has long been known that cardiac failure may complicate the early stages of acute nephritis. Goodhart called attention to this in 1879 and reported patients who had died with pulmonary oedema. Since then numerous observers have described heart failure in this condition, (4, 5, 9, 12, 16, 20, 24), at first as a rare complication, but more recently as occurring with some degree of frequency. The recent articles of Ellis (2), of Rubin and Rapoport (18), and of Marcolongo (13) lay some stress upon the temporary enlargement of the heart which may occur; while Master, Jaffe and Dack (14), Langendorf and Pick (10), Silva, Noguès and Forero (19), and Tur (23) have described the electrocardiographic changes which have been observed at this period. The literature upon the entire subject of cardiac failure in acute nephritis has been excellently and completely recorded within the last few months by Langendorf and Pick (10).

For a number of years during a continuous study of acute nephritis we have been frequently impressed by the clinical evidences of heart failure which are presented by many patients during the acute stage of hemorrhagic nephritis. It has been our custom to employ digitalis in the treatment of these patients, with results which appeared to be beneficial. The comparative frequency of these symptoms, the possible influence that acute heart failure might have upon the course of the disease, and the obscurities that are involved in its etiology and mechanism, led us to devote some study to the problem. The present communication deals with the clinical features of circulatory failure in these patients, with the frequency with which these symp-

toms occur, and with the form of disease in which they are most common.

The methods that have been employed are those usual in clinical observation. More recently changes in the size and shape of the cardiac shadow have been recorded by repeated teleoroentgenograms, and the venous pressure has been measured during the course of the acute illness by the direct method, zero representing a point 5 cm. below the sternum at the level of the second interspace. Readings above 100 mm. of water were considered abnormal. The electrocardiograms made at frequent intervals from these patients are now being studied by one of us (Williams).

The studies have been confined to one large group of cases of acute nephritis, namely those cases in which the nephritis closely followed a more or less severe infection, such as acute tonsillitis or scarlatina. This is a form of glomerular nephritis or hemorrhagic Bright's disease that, for a number of reasons, considered in some detail in previous communications, can usually be differentiated from a second group in which the onset of the disease is insidious and is not preceded by any infection of which the patient is aware.

For the sake of convenience the cases have been divided into three groups: first, those in which the symptoms at onset were mild; secondly, those in which the symptoms were moderately severe; and thirdly, those in which they were very severe. As an indication of the basis upon which this separation was made it may be said that in the severely affected group, headache, nausea and vomiting were common at onset, oedema was often very marked and developed rapidly, the blood pressure was usually much elevated, and there was sometimes anuria at onset. In a few patients convulsions occurred, and in a few hemorrhages and exudates were found in the retina. Albuminuria varied in intensity, but haematuria was always very marked. Renal insufficiency as measured by the excretion of phthalein, the retention of non-protein nitrogen, and the urea clearance, was sometimes present. Some of these features were absent and others less intense in the group designated moderately severe, while all of them except for the albuminuria, cylindruria, and haematuria, were absent or comparatively fleeting in the group classed as mild.

The entire study deals with the conditions observed in 138 patients, in 35 of whom the disease was mild, in 44 moderately severe, and in 59 severe and sometimes fatal. Many of these patients were seen during the first few days of the active stage of their nephritis; 67 or 48.5 per cent were seen during the first week; 21 additional patients before the end of the second week; and 14 more before the end of the third week. Thus, almost half of all the patients were seen during the first week of the disease, and 102 (73.9 per cent) were observed before the end of the third week. The onset of the first symptoms of nephritis was preceded in about 80 per cent of the patients by more or less severe infections of the tonsils or respiratory tract. Scarlatina, infections of wounds or of the skin, and erysipelas were the precipitating infections in the remainder. Cultures were made from the infected areas in 131 cases, and beta haemolytic streptococci, sometimes in combination with minute haemolytic streptococci were found in 128 (97.7 per cent).

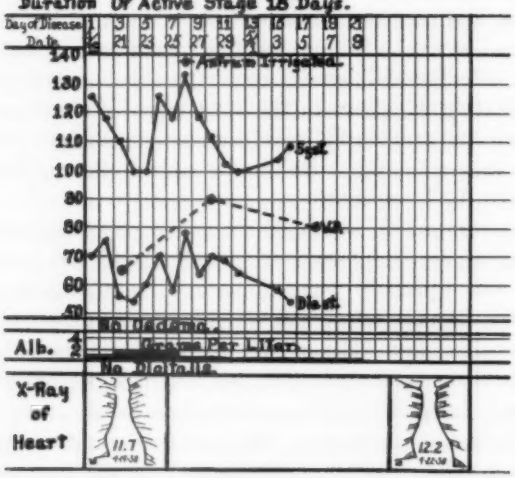
The symptom which indicated to us the possibility of some circulatory failure was dyspnoea, particularly when it was paroxysmal or nocturnal and especially when it occurred in the absence of large pleural effusions and ascites, and when it was combined with orthopnoea. The signs were râles at the bases of the lungs, distension of the veins in the neck, a heaving impulse over the precordium, forceful apical thrust, palpable shocks, enlargement of the area of cardiac dullness, increased intensity of the cardiac sounds, the presence of murmurs or gallop rhythms, enlargement of the liver, sudden accentuations of the subcutaneous oedema, particularly when the latter was combined with lethargy, or convulsive seizures associated with increased pressure of the cerebro-spinal fluid, and pulmonary oedema.

MILD ACUTE NEPHRITIS

The first group consists of 35 patients, or about one quarter (25.3 per cent) of the entire number. In these patients the nephritis appeared to be mild, which is evident from the fact that in 13 of the 35 patients there was no history of oedema, none was observed on physical examination, and no abnormal elevation of blood pressure was recorded. In the remaining 22 cases headache, nausea and vomiting occurred occasionally at onset. Oedema was ascertained

from the history or in the physical examination to be present in 19, while an elevation of the blood pressure above 140 mm.Hg systolic was observed in 13. In none of them did the systolic blood pressure reach 200 mm.Hg, and in only one was the diastolic pressure over 100 mm.Hg.

Chart I



In this, and in the following charts systolic (*Syst.*) and diastolic (*Diast.*) blood pressure are recorded in mm. Hg; venous pressure (*V.P.*), in mm. water; body weight (*Wt.*), in pounds; urinary protein (*Alb.*), in grams per liter; blood non-protein nitrogen (*N.P.N.*), in milligrams per 100 cc. Digitalis dosage is recorded in grams per day, of the powdered leaf. The large figures in the tracings of the teleoroentgenogram indicate, in centimeters, the transverse diameter of the heart.

In none of the patients in this first group was any symptom indicative of circulatory failure actually a striking feature of the disease. In a few of the 13 patients who showed neither oedema nor elevation of blood pressure we have fairly complete records, and Chart I shows that the disease may run its entire acute course without

any evidence of disturbances of the circulation.[1] In the remaining 22 cases of this group oedema occurred in 19, a systolic blood pressure elevated above 140 mm.Hg in 13, and dyspnoea at onset in 4. A small pleural effusion occurred in one case. Some clinical evidence of enlargement of the heart was present in 6; exaggerated precordial impulses were present in 3; increased intensity of the heart sounds occurred in 8, while systolic murmurs were heard in 11. Enlargement of the heart was noted by x-ray in 3 of 8 cases in which serial teleoroentgenograms were made. In none was gallop rhythm noted. In 7 the liver was readily palpable. In addition to albuminuria, cylindruria, and haematuria, there was some evidence of renal insufficiency in a small proportion, for the 2-hour excretion of phthalein was below 40 per cent in 7 of 34 patients, the non-protein nitrogen of the blood was above 50 mg. per 100 cc. in 4, and the urea clearance was below 60 per cent of normal in 6 of the 11 cases in which it was determined.

Chart II shows the changes in blood pressure, body weight, and the teleoroentgenograms in one of the 6 patients in this group having enlargement of the heart, a man of 41, whose early symptoms were dyspnoea, hypertension, and oedema. Unfortunately the patient was not seen until the nineteenth day of disease, at which time there was no dyspnoea or oedema; but even at this time there was still some evidence of cardiac enlargement, and the transverse diameter of the heart in the teleoroentgenogram was 14.8 cm. It is therefore possible that other evidences of myocardial failure may have occurred at the time of his dyspnoea. Nineteen days after his admission to the hospital and on the 38th day of his illness, when the blood pressure had returned to normal, the transverse diameter of the heart in the

[1] The heart outlines on these charts were traced from the teleoroentgenograms, the tracings were then photographed and reduced equally to one sixth the original size. These photographs were then attached to the charts which subsequently were further reduced for publication. The clavicles and the posterior rib outlines have been included, so that the levels of the diaphragm may be compared. In some cases there were significant changes in this respect, notably in Charts VI, VIII and XI, but the variations in level were in no instance sufficient to account for the increase in transverse diameter of the heart.

teleoroentgenogram had decreased to a width of 13 cm., a decrease of almost 2 cm.

From the recorded data it seems clear that a small proportion of patients suffering from acute hemorrhagic nephritis, even in a mild form, may present some of the evidences of circulatory failure, for 6 in this group showed evidences of an enlarged heart associated with oedema and hypertension. Dyspnoea occurred in one other patient

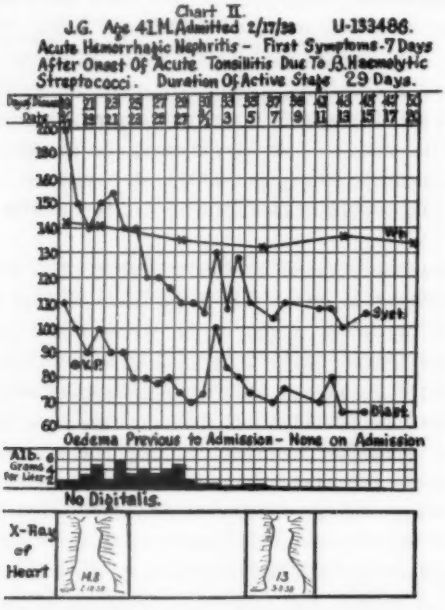


Chart II.
J.G. Age 41 M. Admitted 2/17/38 U-133486.
Acute Hemorrhagic Nephritis - First Symptoms-7 Days After Onset Of Acute Tonsilitis Due To β. Haemolytic Streptococci. Duration Of Active State 29 Days.
Oedema Previous to Admission - None on Admission
Alb. Grams per Liter
No Digitalis.
X-Ray of Heart

in whom the heart did not seem to be enlarged and in 2 additional patients who had oedema but not hypertension.

It is probable that 12 patients in this group presented some symptoms or signs of circulatory insufficiency, but often in such a mild form that they might not be recognized unless one was aware of the possibility of their presence. Determinations of venous pressure were made in only two of these patients. In both it was within normal limits.

The acute phase of the disease lasted for less than three weeks in

12 of the 35 patients. 21 of the 35 patients are entirely well, while 7 others, observed for less than one year, have been in a quiescent stage. Only 2 have progressed over a period of 4 and 6 years, respectively, to a chronic but asymptomatic stage of the disease.

MODERATELY SEVERE ACUTE NEPHRITIS

The number of patients whom we considered to be suffering from a moderately severe form of acute hemorrhagic nephritis was greater than that in the first group. There were 44 patients comprising 31.9 per cent of the entire number of 138. 26 (59.0 per cent) were under 31 years of age. Nausea, headache, and vomiting were common at onset. All but one patient had oedema, sometimes of considerable extent, involving the entire body. The blood pressure was elevated in 35 (79.5 per cent), and in two of these the systolic pressure was above 200 mm.Hg. In 21 the diastolic pressure was 100 mm.Hg or above.

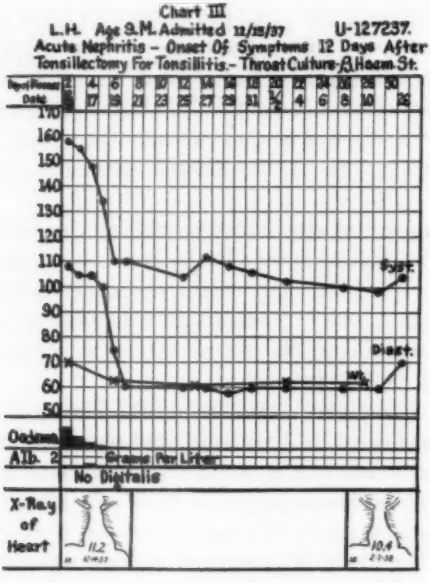
Symptoms suggesting circulatory insufficiency or failure were much more common in this group than in the first. Dyspnoea was an early symptom in 21 or almost half of the cases. It occurred in paroxysmal attacks in 2 cases. Orthopnoea was present in 2 cases. Obvious effusions of fluid into the pleural cavities were found in 3 patients and ascites was present in one.

The veins of the neck were frequently engorged. The venous pressure was measured in 7 patients, and was found to be elevated in 5 of these, returning to a normal level as the acute illness subsided. The cardiac dullness was enlarged in 27 or over 60 per cent; in 18 of these the shape and size of the cardiac shadow were followed during the course of the illness by means of teleoroentgenograms, 12 (66.6 per cent) showing enlargement during the acute stage. The cardiac impulses were noticeably forceful in 18, the sounds were exaggerated in 28, and systolic murmurs were heard in 14. In three patients there was a gallop rhythm. We have estimated roughly from clinical symptoms and signs that some evidence of circulatory insufficiency or failure occurred in 33 of the 35 patients.

In many of these patients the evidences of circulatory failure appeared to be out of all proportion to the severity of the nephritis, as measured by the amount of albumen, the number of casts and red

blood cells in the urine, or evidences of renal insufficiency. This situation is illustrated in Charts III and IV.

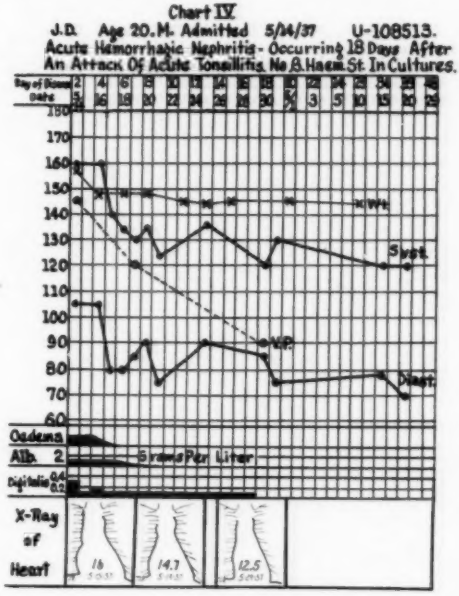
The condition of the young colored boy, 9 years of age (Chart III), appeared to be essentially one of hypertension with enlargement of the heart, and circulatory failure. The oedema was fairly well marked, but the albuminuria was almost insignificant, and the haematuria and cylindruria only of slight degree. The excretion of phthalein, the non-protein nitrogen of the blood, and the urea clear-



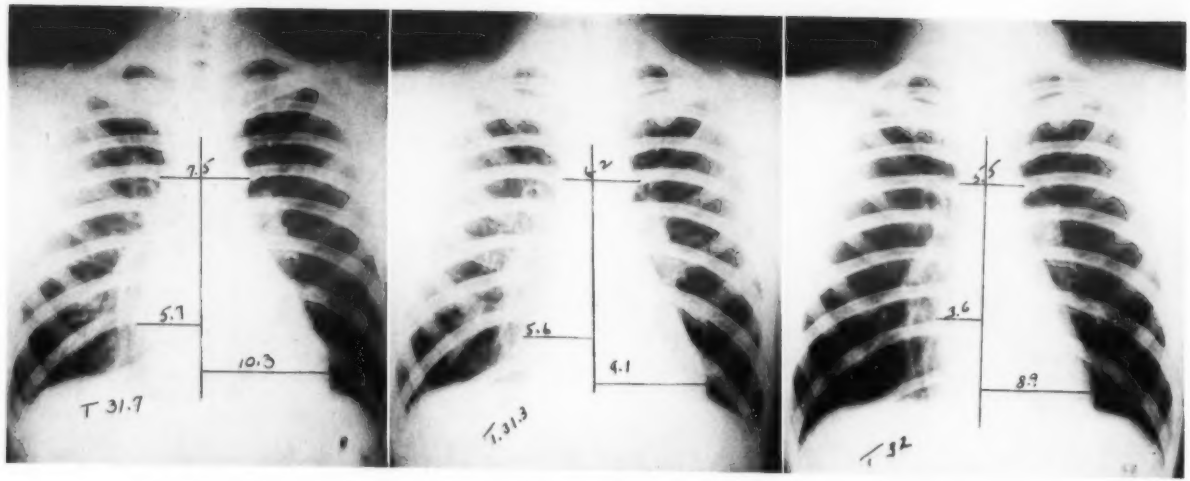
ance were within normal limits. Dyspnoea was a prominent feature, and the liver was enlarged. The condition might well have been mistaken for vascular hypertension, cardiac hypertrophy, and myocardial failure. Unfortunately no determinations of the venous pressure were made. The subsequent course of the illness proved quite characteristic of acute hemorrhagic nephritis.

In another young white man of 20 (Chart IV, fig. 1) the dyspnoea at onset, the enlargement of the cardiac shadow (16 cm. transverse

diameter in teleoroentgenogram), and the elevation of the venous pressure were somewhat disproportionate to the apparent severity of the nephritis. He was seen on the second day after the onset of his illness. Chart IV shows graphically the degree of elevation of arterial and venous blood pressures, the enlargement of the heart, the extent of the oedema, and the degree of albuminuria. Haematuria was profuse, but the phthalein excretion was 69 per cent in 2 hours, the non-protein nitrogen of the blood 34 mg. per 100 cc., while the urea



clearance was 113 per cent of normal. The chart shows the rapid changes which occurred during five days rest in bed, combined with administration of digitalis. By the seventh day of his disease the oedema had practically disappeared, the albuminuria had diminished, and the arterial pressure had fallen; but the venous pressure was still comparatively high, and the heart had not reached normal size, the transverse diameter being 14.7 cm. Ten days later, on the seventeenth day of his disease, the size of the cardiac shadow had decreased

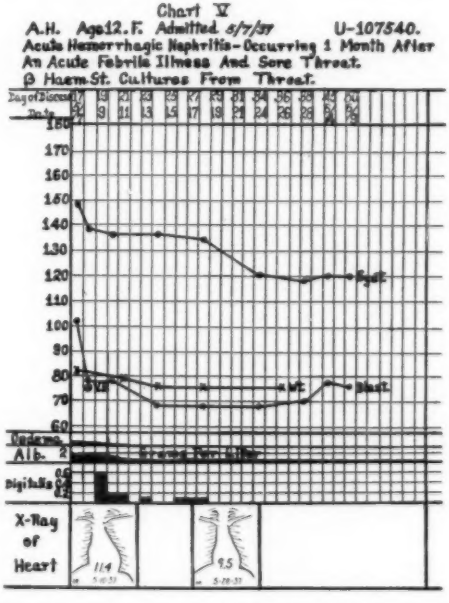


May 17, 1937 May 19, 1937 May 29, 1937

FIG. 1. *J. D. Serial Teleroentgenograms,* from which the tracings on Chart IV were made, showing not only a decrease in the transverse diameter of the heart but also a decrease in the width of the great vessel shadow, and in the lung root markings.

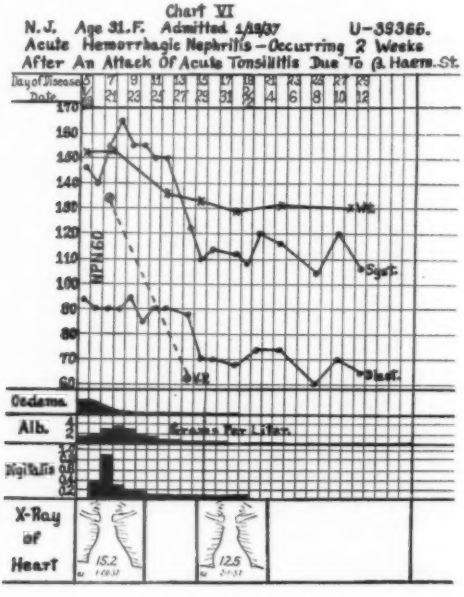
remarkably, so that the transverse diameter was 12.5 cm., a reduction of 3.5 cm. At this time he was symptomatically well, though the urine continued to show albumen and red blood cells.

It has frequently been noted that recession of the cardiac enlargement takes place comparatively slowly. Chart V illustrates this. With comparatively little oedema and albuminuria, with a normal venous pressure, but with an elevated arterial blood pressure, the size of the heart in this girl of twelve, who was first seen on the seven-



teenth day of her illness, was at this date still increased in size; the transverse diameter measuring 11.4 cm. Ten days later, on rest in bed and digitalis, and with the fall in blood pressure, a considerable reduction had taken place in the size of the cardiac shadow, for the transverse diameter at this time, on the thirtieth day of the disease had decreased almost 2 cm. to 9.5 cm. The chart shows very well the gradual reduction in the size of the cardiac shadow, following the fall in arterial pressure and the disappearance of oedema.

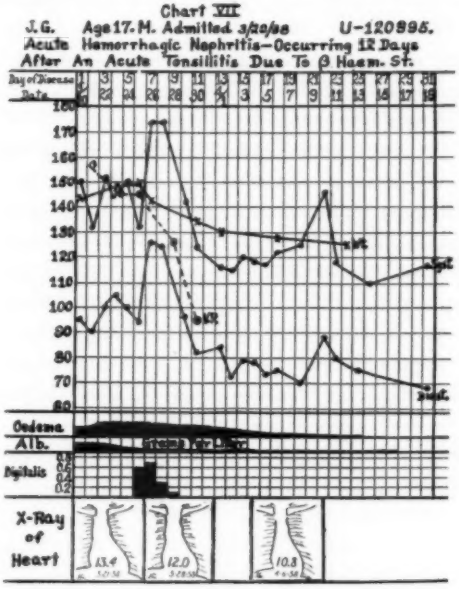
A somewhat different course was observed in the following cases, illustrated in Charts VI and VII. In a woman of 31, whose first symptoms appeared 2 weeks after an attack of acute tonsillitis caused by the beta haemolytic streptococcus, dyspnoea and oedema were prominent. In addition to the anasarca, there was a pleural effusion. In this patient the non-protein nitrogen of the blood was distinctly elevated (60 mg. per 100 cc.), though renal functional tests were normal (Phthalein excretion 88 per cent in 2 hours; urea clearance



84 per cent of normal). On the seventh day of the disease the arterial blood pressure rose, the oedema became more marked, and the albuminuria increased. The venous pressure was elevated. On the previous day the transverse diameter of the heart was 15.2 cm. Digitalis was administered, and within a week the arterial and venous blood pressures had fallen to normal and the oedema had disappeared. On the eighteenth day of disease, when the second teleoroentgenogram was made, the transverse diameter of the heart was 12.5 cm., a reduction of 2.7 cm. in 12 days.

The course of the disease in this patient illustrates a series of events which will be referred to again in a discussion of the third or severe group, for particular interest is attached to the cases showing a sudden progression of symptoms after admission to the hospital; but it is desirable to emphasize the matter by quoting another example from the present group, of this particular variation in the course of the disease.

A colored boy of 17 (Chart VII) was admitted to the Johns Hopkins Hospital within 24 hours of the onset of headache, nausea, dyspnoea,



and oedema following a severe attack of tonsillitis 12 days previously. The arterial blood pressure was elevated and the day after admission the venous pressure was found to be 157 mm. of water. The heart showed a diameter of 13.4 cm. in the teleoroentgenogram. The oedema was moderate, involving the face as well as the body. The cervical veins were distended. There were visible impulses over the precordium, with faint systolic and diastolic shocks. Dullness in the fifth interspace was 9 cm. to the left. The first sound at the apex

was pronounced, and a faint systolic murmur was heard in the pulmonic area. During the next five days there was an increase of oedema and in weight, and the venous pressure remained elevated. On the seventh day of disease he was nauseated and drowsy, and the blood pressure suddenly rose to 174 mm.Hg systolic and 126 mm.Hg diastolic. It was obvious that serious symptoms threatened, and on this day digitalis was administered in comparatively large doses. Within the next four days the symptoms improved; the arterial pressure and venous pressure fell almost to normal, the oedema decreased, the weight was reduced, and the diameter of the heart shadow decreased 1.4 cm.

The few charts selected as protocols to illustrate the condition of the circulatory apparatus during the course of the acute nephritis in this group of moderate severity, furnish evidence of derangements that are not only of theoretical but of practical importance. A study of this group of patients leads to the conclusion that there were symptoms and signs to indicate at least some degree of circulatory insufficiency in 33 of the 35 cases. In only 7, however, were these sufficiently severe or prominent to justify the designation of circulatory or myocardial failure. The patients who were the subjects of Charts VI and VII must be included amongst these. From our experience, it appeared that the evidences of circulatory failure were so definite that digitalis was necessary in the treatment of their illness.

In this group of 44 patients suffering from a moderately severe form of the disease, 20 (45.4 per cent) are at the present time entirely well, 20 are in a latent stage of the disease, and of these only 3 have been followed for more than a year, so that undoubtedly a considerable proportion of the latent cases will recover. Three patients have progressed to a chronic stage of the disease and one patient has died in uraemia.

SEVERE ACUTE NEPHRITIS

The third and largest group of 59 patients suffered from nephritis in a severe form. This group presents a somewhat different problem from the other groups. The severity of the illness in many of these patients, when they were admitted to the hospital, was due as much

to the primary or complicating infection from which they suffered, as to the intensity of the nephritis. This is reflected in the mortality, for 12 patients died primarily of the infection during the acute illness. Secondary pneumonia was responsible for three of these deaths. We have, however, considered the group as a whole even though it was impossible to determine what part the acute infection played in producing the symptoms of circulatory failure.

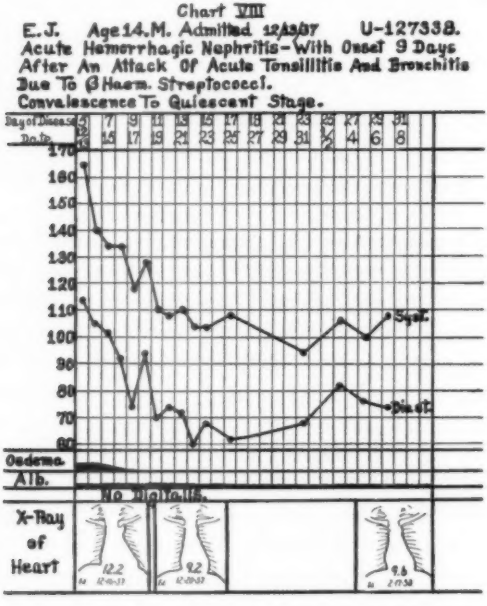
In about half of the patients headache, nausea, and vomiting were early and marked symptoms. 54 of the 59 patients showed oedema; 12 had pleural effusion; 10 had ascites; 3 had pulmonary oedema; and 3 had cerebral oedema. X-ray pictures of the chest of many of these patients showed diffuse shadows extending into the lung fields from the hilum, such as are so frequently seen in x-rays of patients with myocardial failure. The shadow of the great vessels was often widened towards the right, suggesting dilatation of the superior vena cava.

Dyspnoea was common. It was actually observed on admission to the hospital in 24 patients or 40.6 per cent and was present during the course of the disease in 34 or 57.6 per cent of the patients. Dyspnoea was paroxysmal in one patient. Orthopnoea occurred in 5 (2 history, 3 examination). The cardiac dullness was increased in 39 or 66.1 per cent. Of 17 cases having two or more teleoroentgenograms, 13 or 76.4 per cent showed enlargement during the acute stage. The impulses were forceful in 27; the sounds were exaggerated in 40 or 67.8 per cent; and murmurs were present in 35. Gallop rhythm, a sign which we have considered to be of considerable importance, was detected in 11 or 18.6 per cent. The venous pressure was elevated in all of 7 cases in which it was measured. The systolic arterial blood pressure was above 140 mm.Hg. in 51 or 86.4 per cent; in 7 of this number (11.8 per cent of the patients) it was above 200 mm.Hg. The diastolic blood pressure was 100 mm.Hg. or above in 39 of the 59 patients. The liver was enlarged in 20 cases, or over one-third of the number.

In addition to the marked albuminuria, cylindruria, and haematuria, evidences of renal insufficiency were much more common than in the other groups. Oliguria or transient anuria occurred in several patients. The excretion of phthalein was reduced below 40 per cent

in 2 hours in 17 of the 54 cases in which it was determined (31.4 per cent). The non-protein nitrogen of the blood was elevated above 50 mg. per 100 cc. in 24 of 58 cases (41.3 per cent) and the urea clearance reduced below 60 per cent of normal in 17 of 39 cases (43.6 per cent).

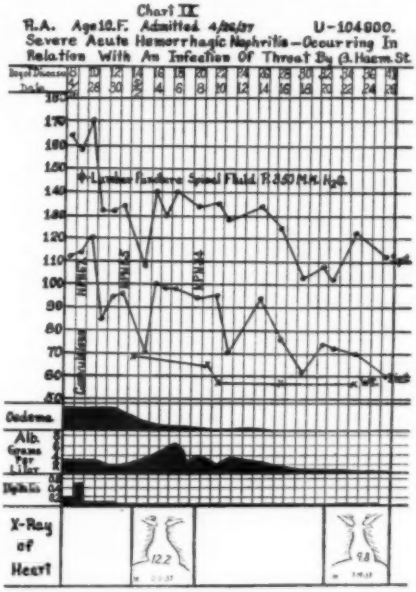
The instance of the young colored boy of 14 years admitted to the Johns Hopkins Hospital on the fifth day of disease, depicted in Chart VIII, illustrates the conditions as they were observed in the mildest



form of the disease in this group. Unfortunately the venous pressures were not recorded, but in combination with slight oedema, albuminuria, and haematuria, there were dyspnoea and excessive hypertension with considerable enlargement of the heart (transverse diameter 12.2 cm.). Almost immediately after admission to the hospital, the blood pressure fell precipitously, the mild oedema disappeared, and on the twelfth day of disease the teleoroentgenogram showed a reduction in the size of the heart to a diameter of 9.2 cm.,

a change of 3.0 cm. in diameter in four days. This case is illustrative of the fact that in these patients, as well as in those having a moderately severe attack of acute nephritis, enlargement of the cardiac shadow and dyspnoea may be prominent even in patients with very little oedema and very slight albuminuria.

Reference has already been made to the fact that in some patients there was a rather sudden increase in blood pressure, oedema, malaise, headache, and sometimes nausea, shortly after their entry into the hospital. These symptoms and signs are usually unfavorable ones.

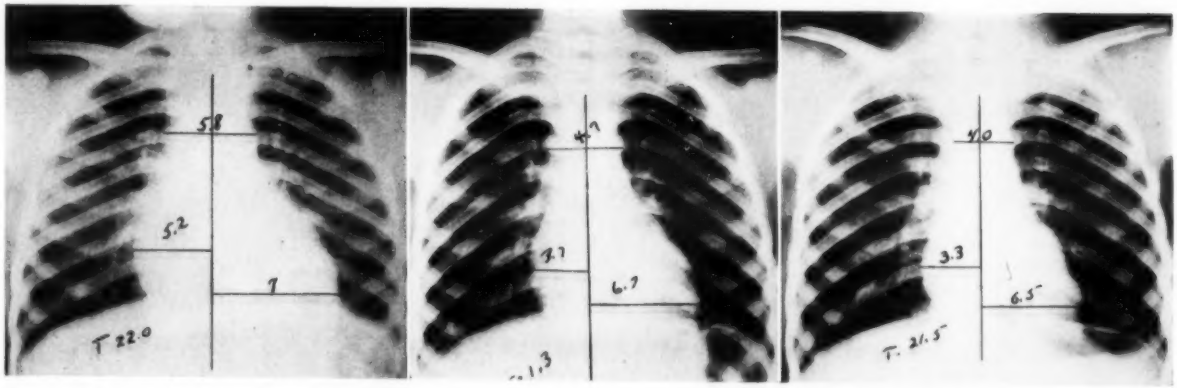


The course of the disease in a case of this type, and the rôle that may be attached to insufficiency of the circulatory system in precipitating these symptoms, is exemplified by the following case illustrated by Chart IX.

This colored girl of 10 was admitted to the Johns Hopkins Hospital 8 days after the onset of headache, nausea, and oedema. 24 hours after admission her condition suddenly became grave. She grew

drowsy, the blood pressure rose, there was dyspnoea and convulsive seizures. Unfortunately a determination of the venous pressure was not made, but a lumbar puncture showed the spinal fluid to be under a pressure of 350 mm. of water. The area of cardiac dullness was increased to a diameter of 12 cm.; the impulses were forceful, the sounds loud, and there was a gallop rhythm. On the administration of digitalis, intramuscular injections of magnesium sulphate, and intravenous injections of sucrose, she improved very rapidly. Nine days after admission, the seventeenth day of illness, a teleoroentgenogram showed the cardiac diameter to be 12.2 cm. At this time the blood pressure was still somewhat elevated, and the oedema had not entirely disappeared. By May 21, the thirty-fifth day of illness, the patient was convalescent, but on July 6, the area of cardiac dullness was still large, the diameter of the cardiac shadow being 10.4 cm. By July 19, however, the heart appeared normal and the diameter by teleoroentgenogram had decreased to 9.8 cm., a decrease of 2.4 cm. from the first measurement. At the present time the patient is in a quiescent asymptomatic stage of the disease.

An even more striking example of this form of the disease is furnished by a somewhat similar case illustrated in Chart X. On admission this colored girl of 12 showed evidences of severe renal insufficiency, with 128 mg. of non-protein nitrogen per 100 cc. of blood. The blood pressure was normal. Within 48 hours after admission the blood pressure had risen, the oedema had increased, and the patient became drowsy. The area of cardiac dullness reached 10.5 cm. to the left in the 5th intercostal space; the impulses were forceful; there was a gallop rhythm, and a systolic murmur at the apex. The transverse diameter of the cardiac shadow was 11.7 cm. On the tenth day of disease the venous pressure measured 215 mm. of water. Signs of pulmonary oedema appeared. There was one convulsion. The spinal fluid pressure measured 410 mm. of water. After the administration of digitalis, magnesium sulphate intramuscularly, and sucrose intravenously, her condition rapidly improved. Five days later the arterial and venous blood pressures were normal and the oedema had practically disappeared; she had lost 16 pounds in weight and was convalescing satisfactorily. The heart, however, remained somewhat enlarged for months, and it was

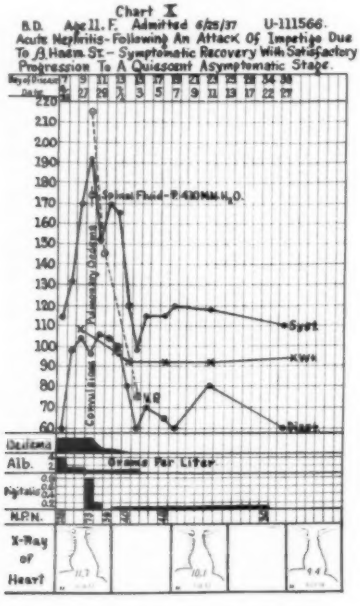


May 5, 1937 July 6, 1937 July 19, 1937

FIG. 2. *R. A. Serial Teleoroentgenograms*, from which the tracings on Chart IX were made, showing the progressive decrease in the transverse diameters of the heart.

not until a year after admission that it reached a comparatively normal diameter of 9.4 cm., a decrease from the original measurement, of 2.3 cm.

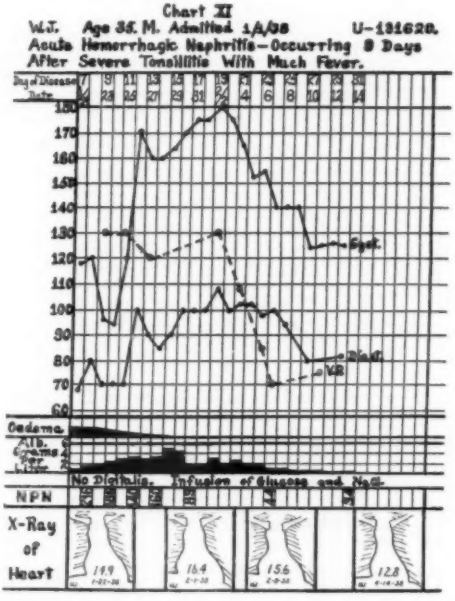
In such instances as these, with the enlargement of the heart and the pronounced evidences of myocardial failure, one cannot escape the conclusion that the profound circulatory disturbances have an important bearing upon the sudden appearance of such alarming conditions as pulmonary oedema and cerebral oedema.



It also seems probable that the administration of digitalis has some beneficial effect, for the following case (Chart XI), though not as serious as the two just recorded, indicates that without the use of digitalis, the period of hypertension, of cardiac enlargement, and of circulatory insufficiency may be prolonged.

When this white man of 35 was admitted to the Johns Hopkins Hospital 7 days after the onset of his illness, he was desperately ill, with suppression of urine and with a blood non-protein nitrogen of

216 mg. per 100 cc. The arterial blood pressure was normal, or rather low, but the venous pressure on the ninth day of disease was definitely, though moderately, elevated. The heart dullness was percussed 10 cm. to the left, but the sounds were not remarkable. Three days later the blood pressure suddenly rose, reaching its peak on the nineteenth day of illness. The venous pressure remained at 130 mm. water. At this time the cardiac shadow had increased from 14.9 to 16.4 cm. in diameter. It is to be noted, however, that the



diaphragm in the tracing made from the x-ray on February 1, was higher than in the first teleoroentgenogram. This may have caused elevation of the heart with some widening of the cardiac shadow. During the following 10 days the venous pressure fell, somewhat more rapidly than the arterial pressure, but not until the twenty-seventh day of illness were both pressures normal. By this time the oedema had disappeared, but the cardiac shadow still measured 15.6 cm. in diameter. Five teleoroentgenograms were made between this time

and April 14, a period of 2 months, when the transverse diameter of of the shadow finally reached 12.8 cm., a reduction of 3.6 cm. from the widest diameter. This patient did not receive digitalis and one wonders whether the long period of moderate circulatory insufficiency and cardiac enlargement might have been shortened by the use of this drug.

A final matter which has not yet been mentioned, is the effect which an attack of acute hemorrhagic nephritis exerts upon the cir-

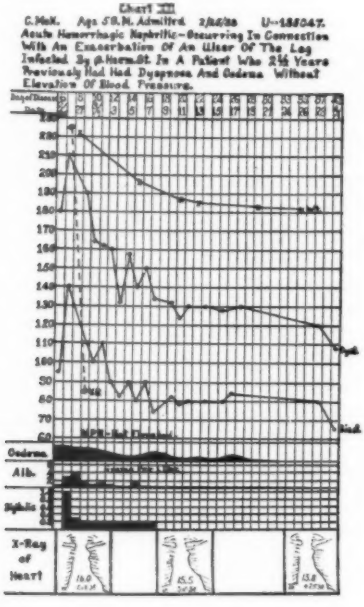


Chart XII
C. McK. Age 59 N. Admitted 2/26/20 U--185047.
Acute Hemorrhagic Nephritis--Occurring In Connection With An Exacerbation Of An Ulcer Of The Leg Infected By β Hæm. St. In A Patient Who 2½ Years Previously Had Had Dyspnoea And Oedema Without Elevation Of Blood Pressure.
Oedema
Alb.
Syphilis
X-Ray of Heart

culation of an individual who has some form of chronic heart disease. A few such instances have come under observation, but in this group the following case (Chart XII) forms a striking example of the degree of myocardial insufficiency that may occur under these circumstances.

The patient was an elderly colored man, 59 years of age, who was known to have had periods of dyspnoea and oedema of the feet in the past, without any elevation of blood pressure. Following an acute exacerbation of an ulcerative infection of the leg, due to beta haem-

olytic streptococci, he developed headache, oedema and severe dyspnoea, with orthopnoea. He was admitted to the Johns Hopkins Hospital on the sixth day of his illness in great respiratory distress. In addition to the extensive oedema there were marked hypertension, enlargement of the cardiac shadow (transverse diameter 16 cm.), a systolic murmur at the apex, and a venous pressure of 220 mm. water. There was well marked albuminuria, cylindruria, and haematuria, but the functional tests were within normal limits: phthalein excretion 61 per cent in 2 hours; N. P. N. 32 mg. per 100 cc.; urea clearance 62 per cent of normal.

It was difficult to determine, when he was first admitted, whether he was suffering exclusively from myocardial failure, or whether the symptoms of myocardial failure were secondary to nephritis. The subsequent course of events, as depicted in Chart XII, showed conclusively that the disease was primarily acute hemorrhagic nephritis from which he recovered symptomatically with great rapidity. With rest in bed, digitalis, and sulfanilamide, given for the infected ulcer of the leg, the venous pressure fell to normal within 48 hours, but the arterial pressure and weight declined more slowly, while the oedema gradually disappeared. The leg ulcer healed promptly. By the twentieth day of the disease, 2 weeks after admission, the patient was symptomatically well, though albumen and red blood cells still persisted in the urine. The diameter of the cardiac shadow did not reach normal until two months after admission, when it measured 13.8 cm., a reduction of 2.2 cm. from the measurement on admission.

It must be concluded that, in this patient, the serious myocardial failure was precipitated by the attack of acute nephritis. It is probable, however, that the heart was not entirely normal before the occurrence of the acute nephritis, and that a moderate degree of arteriosclerotic heart disease predisposed him to the exaggerated effect which was observed.

There are eight other patients in this entire collection of 138, in whom some form of heart disease existed at the time of the onset of acute hemorrhagic nephritis. In one woman who had a questionable lesion of the mitral valve, the nephritis was mild, and there was neither oedema nor dyspnoea. In one other patient, a boy with a questionable rheumatic lesion of the mitral valve, whose acute attack

of nephritis was moderately severe with elevation of blood pressure, there was only slight oedema and no dyspnoea; but in a man with outspoken mitral stenosis and insufficiency in this same group, marked oedema, dyspnoea, orthopnoea, and cyanosis occurred. Both of these patients recovered and are now entirely well. In four other patients, three with chronic rheumatic heart disease involving the mitral valve, and one with hypertension of some years' duration, the acute attack of nephritis was severe; and in all the oedema and dyspnoea were of unusual intensity. One of these patients recovered from the nephritis, in one the disease has progressed satisfactorily to a latent stage, and two patients died during the active stage of the disease.

The occurrence of some signs of myocardial failure in this group of 59 patients with severe acute hemorrhagic nephritis was very frequent, since 53 of the 59 presented some evidence of circulatory failure. The proportion of cases in which this was a predominant feature of the disease, as may be seen from the illustrative protocols, was also much greater than in any other group. Thus the experience derived from a study of this group of cases of severe acute nephritis served to emphasize the importance of circulatory failure as a condition, which must be regarded not simply as a complication, but in many patients, as an essential part of the disease.

The death rate in this group of 59 patients was very high (12 patients, or 20.3 per cent), and a fair proportion of these died in the active stage of the disease, often, as one reviews the situation, with definite symptoms of circulatory failure. The number of complete recoveries, *pari passu*, in comparison with those in the other groups, is small (27.1 per cent). It appears that the immediate danger in the active stage of acute hemorrhagic nephritis comes from the severity of the acute infection and the gravity of the circulatory failure, while a progression of the nephritis to a chronic stage is always threatened when the infection persists, even in a latent form.

DISCUSSION

From these studies we have concluded that cardiac insufficiency is a fairly frequent accompaniment of acute glomerular nephritis. We believe that approximately 98, or 71 per cent, of the series of

138 cases showed clinical signs of cardiac insufficiency. This is a somewhat higher percentage than that usually reported in other comparatively large series. Marcolongo (13) reports cardiac insufficiency in 40 per cent of 80 cases, Master (14) 33 per cent of 24 cases, Rubin (18) 25 per cent of 55 cases, Ellis (2) 20 per cent of 100 cases, and Murphy (15) 17 per cent of 94 cases. It has been the experience in this clinic, as in others, that evidence of cardiac insufficiency will be found in direct proportion to the care with which it is looked for, and this may account to some extent for the higher figure given for this series. The evaluation of signs and symptoms in the borderline cases provides another source of possible difference. Thus a single x-ray picture taken during the early stage of acute glomerular nephritis may show a heart the transverse diameter of which is within the classical normal limit, *i.e.*, less than one-half the internal diameter of the chest. Yet subsequent roentgenograms of this heart, which is reported by the roentgenologist as being of normal size, may show a reduction of several centimeters in transverse diameter as well as some change in the shape of the shadow. The alterations in the shape of the cardiac shadow appear to be of some significance. A rounded contour often gave place to a more elongated shadow, even though the diaphragm remained at the same height. In addition to this, the shadow of the great vessels, which was often widened to the right during the early stage of the acute nephritis, became narrower as convalescence was established. This increase in the shadow to the right was interpreted as being due to a dilatation of the superior vena cava. In many of the teleoroentgenograms made during the acute phase, diffuse shadows, such as are seen in patients with myocardial insufficiency, extended from the roots to the mid lung fields.

For the demonstration of changes in the electrocardiograms, which occur in many cases of acute glomerular nephritis, it is often necessary to have several records. We have also found that repeated determinations of the venous pressure will give accurately measurable evidence of congestive failure of considerably greater value than the more indefinite clinical manifestations.

It is evident from the observations made in this series of cases that myocardial failure is not only a fairly frequent accompaniment of

acute glomerular nephritis, but that in a large group of cases it varies in its severity in direct proportion to the severity of the nephritis. Thus in Group I (mild cases) 12 of the 35 patients showed some evidence of cardiac insufficiency; in Group II (moderately severe cases) 33 of the 44 patients; and in Group III (severe cases) 53 of the 59 patients. For the individual case, however, this correlation does not hold true, for occasionally myocardial failure may dominate the clinical picture, the nephritis being comparatively mild, or it may even be the presenting symptom. This would seem to hold true for adults, but may not be so in the case of children. In a recent review of 55 cases of acute glomerular nephritis in children Rubin and Rapoport considered 14 cases to have signs of definite myocardial damage, but contrary to our experience, they were unable to demonstrate any correlation between the occurrence of signs of cardiac failure and the severity of the renal manifestations.

From the time of Goodhart (6, 7), writers have attempted to explain the origin of the cardiac enlargement and myocardial failure in these patients. Langendorf and Pick (10) have discussed these hypotheses at length. It seems highly improbable that the enlargement of the teleoroentgenographic shadow is due in any large part, as Alwens and Moog (1) have suggested from their orthodiagraphic study, to an accumulation of fluid in the pericardial sac. Though this might give rise to effects, similar to many that are observed, yet the persistence of the enlargement for days, weeks, or even months after the oedema had disappeared and the arterial and venous pressures have returned to normal, render Alwens and Moog's conjecture highly improbable.

There are, however, two other factors of primary importance. One is the hypertension and the other a hypothetical myocardial damage. That the hypertension is a potent factor in the production and accentuation of cardiac failure goes almost without saying, and the correlation between the rise in blood pressure and the occurrence of signs of failure has been repeatedly demonstrated.

There are several reasons, however, for introducing a second and unknown factor. Thus, evidence of cardiac failure and enlargement of the cardiac shadow in roentgenograms have been observed during the course of acute glomerular nephritis, in the absence of significant

hypertension (Levy) and even in the absence of any elevation of the blood pressure whatsoever (Murphy). In addition they have been observed to occur before the onset of the hypertension, becoming accentuated thereafter. Chart XI is an example of this. It is true that hypertension may occur early and be fleeting, and thus escape observation at the time the patient presents himself, but any such transient rise in blood pressure cannot be seriously considered in the etiology of cardiac insufficiency. Another observation pointing to a "myocardial factor" is that signs and symptoms of heart failure may be present in cases having only a moderate degree of hypertension, yet these patients are chiefly in the second and third decades when the myocardial reserve is at its maximum. This is illustrated in Charts IV and VII. In addition there is at times no correlation between the degree of hypertension and either the incidence or degree of cardiac failure. It is the impression of all the authors who have studied the electrocardiographic changes in acute glomerular nephritis (10, 14, 19, 23) that the changes found cannot be explained by mechanical factors alone, such as an increase in the size or a shift in the position of the heart, but must indicate an alteration in the condition of the myocardium itself. Recent studies of serial electrocardiograms in some of the cases here reported tend to bear out this conclusion and will be reported later. In addition the electrocardiographic changes, as well as the cardiac shadow, have sometimes been observed to regress only long after the hypertension has disappeared.

It would seem, therefore, that an additional factor beside the hypertension must be involved to explain the picture. There is no clue to the nature of this factor. Damage due to toxins from the antecedent infection could explain at best only a few of the cases, chiefly those occurring after scarlet fever, a disease in which erythrodermic toxins have been demonstrated in the serum. The retention of metabolites forms an equally inadequate hypothesis, as in many cases there is little, and in some instances no elevation of the nonprotein nitrogen of the blood. No information is obtained from microscopic examination of the heart muscle, which is almost universally reported as being normal, or at the best slightly oedematous.

The problem resolves itself into one intimately connected with the pathogenesis of acute glomerular nephritis. On the basis of the

oedema which may occur in the absence of cardiac insufficiency and without significant depression of the plasma protein levels, a widespread capillary damage has been assumed. The total plasma protein values in this series of cases, which will be reported later in detail, were essentially within normal limits, varying from 6.5 to 7.5 gm. per 100 cc. The absolute values for the plasma albumen were, as a rule, relatively low, while the absolute values for the plasma globulin were relatively increased. These changes might result in some reduction of the osmotic pressure. The results which have been reported in the literature on direct observation of the capillaries, and on capillary pressure in acute glomerular nephritis are so contradictory and open to criticism that they have added little to the concept. Yet the evidence has been sufficiently strong for most students of this subject to accept the theory of capillary damage. It is conceivable that the smaller vessels of the myocardium might be involved in this vascular lesion, perhaps by constriction, as Langendorf and Pick have suggested. In some such way as this, extensive temporary damage to the muscle, the results of which are so often observed, might be brought about.

Whatever the actual cause of the myocardial failure may be, the effect which it has upon the acute phase of the disease is likely to be damaging. The results of this disturbance appear to form an essential part of the clinical picture. It is not improbable that circulatory failure, however it arises, may very well accentuate the oedema, or even play some part in giving rise to it. It has certainly appeared that sudden increases in subcutaneous oedema, as illustrated in Case VII, and the occurrence of cerebral oedema, as illustrated in Cases IX and X, was closely associated with severe myocardial failure. The same thing is undoubtedly true of patients having pulmonary oedema.

In other ways, too, the circulatory failure may have a detrimental effect. Under such circumstances, congestion of the kidneys, followed as it usually is by retardation of blood flow, may reduce the output of urine and enhance the renal insufficiency. This always results in a grave situation in cases of acute nephritis. Indeed the function of the kidneys may be impaired in uncomplicated myocardial failure. When myocardial failure is imposed upon a chronic nephritis, the effect may be very serious and actually lead to uraemia.

It has long been the clinical impression that digitalis was effective in the treatment of acute glomerular nephritis when signs of cardiac insufficiency were present, and we have also been impressed for a long time by the fact that rapid decline of arterial and venous blood pressure, loss of weight, decrease of oedema, and diuresis often follows promptly upon the use of digitalis in full doses. The evaluation of any form of therapy in a disease, the acute stage of which runs as short and as variable a course as acute nephritis, is notoriously hazardous. It is, of course, well known that rapid spontaneous improvement frequently coincides with complete rest in bed, combined only with proper control of diet and fluids. Such recoveries are illustrated by Charts III and VIII; but there are some patients in whom this sudden and satisfactory result does not occur. It is in the latter cases, with steadily or rapidly increasing blood pressure, weight, and oedema, as illustrated in Charts VI, VII, IX, X, and XII, that the administration of digitalis has appeared to be of definite benefit. The course which the disease may run when digitalis is not administered, is illustrated by Case XI. The elevated arterial and venous blood pressure, the enlargement of the heart, and, to some extent, the anasarca persisted in this patient for an unduly long period.

CONCLUSIONS

From a study of 138 patients, mostly young adults, suffering from the form of acute hemorrhagic nephritis that follows directly upon an active infection due usually to haemolytic streptococci, it has been observed that circulatory insufficiency often forms an integral part of the illness. It is characteristic that evidences of circulatory failure may appear at the onset or during the first few days of the disease. These manifest themselves as dyspnoea which may become paroxysmal or progress to orthopnoea, by enlargement of the heart, accompanied by alterations in the impulses and sounds, by elevation of venous pressure, and by enlargement of the liver.

The circulatory failure may well lead to an increase of subcutaneous oedema, or to cerebral or pulmonary oedema, and may produce other deleterious effects such as interference with the function of the injured kidneys. These conditions are uncommon in mild attacks of nephritis, frequent in moderately severe attacks, and present in

the majority of cases of severe acute nephritis. The use of digitalis in full doses has seemed to benefit some of these patients with severe circulatory failure.

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THE SIGNIFICANCE OF FIBRILLATION, FASCICULATION AND OTHER MUSCULAR TWITCHINGS WITH SPECIAL REFERENCE TO RECENT PHYSIOLOGICAL INVESTIGATIONS

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Several types of muscular twitchings[1] are recognized by clinical neurologists and great stress is laid upon the importance of proper differentiation of the various types, for some twitchings indicate a progressive and uniformly fatal disease and others have no serious prognostic significance. Unfortunately the different types are not always easy to distinguish and are sometimes incorrectly or incompletely described in standard text-books of neurology. It is the purpose of this paper to offer a brief description of the more common varieties of muscular twitchings and to call attention to recent experimental investigations which have thrown new light upon the causation and physiological significance of such phenomena.

Denny-Brown and Pennybacker have recently published a very interesting and important paper detailing studies in which both mechanical and electrical records were made of several types of muscular twitchings. In the electrical studies, needle electrodes were employed and four-stage amplifiers were used which permitted measurement of minute changes of electrical potential. This paper will be mentioned repeatedly in the following pages for the results are of great interest to clinical neurologists.

TRUE FIBRILLATION

It has long been known that when the twelfth nerve is severed the resulting atrophy of the tongue is associated with a very fine quivering

[1] This term is loosely applied to contractions of parts of a muscle in contrast to contractions of the whole muscle as in other involuntary movements such as myoclonus and athetosis.

of the intrinsic muscles. This observation might suggest that the tongue behaves in a peculiar manner for no such quivering is seen as a rule in the muscles of the extremities when the nerves which supply them are sectioned. The following case history may be cited to illustrate this phenomenon.

Case 1. A middle aged business man became depressed and suicidal as a result of financial reverses. He placed the muzzle of a revolver in his mouth and fired. The bullet passed through his neck without causing him serious injury. The base of the tongue was penetrated and the left twelfth nerve was severed. Some three weeks after the injury examination showed obvious atrophy and wrinkling of the left side of the tongue. The tip of the tongue curved to the left and movements of the tongue toward the left were somewhat limited. Electrical tests showed reaction of degeneration on the left side. Close inspection of the tongue revealed a constant fine quivering on the left side. The movements were very minute and were seen best with a hand lens in oblique light. They were much finer than the twitchings seen in subjects suffering from the common progressive bulbar palsy.

Langley and Kato found that all striated muscles show such quiverings when they are deprived of their motor nerve supply. The movements are so fine, however, that they are not visible unless the muscle is exposed by dissection or is very thinly covered as it is in the tongue. Occasionally in an emaciated individual this quivering may be observed through the skin. The quivering begins on the fifth day after division of the nerve, it is claimed, and persists for a long time, perhaps until the muscle fibers have disappeared. It is believed that the quivering represents true fibrillation; that is, the contractions involve individual muscle fibers and not groups of fibers. These fibrillations, according to Denny-Brown and Pennybacker, recur at intervals of about 2 seconds and each contraction is associated with a very minute, single, diphasic action current. They state that, "the fibrillation is due to a periodic rhythmical twitch excitation of each muscle fiber sensitized by neural atrophy." The source of this excitation is not entirely clear but for various reasons the authors suggest that the small amounts of acetylcholine present in the normal circulation may be the exciting agent. Fibrillations are not seen in the various types of myopathy.

SPONTANEOUS FASCICULATION

Twitchings of this type are usually incorrectly termed *fibrillations* thought they are obviously too coarse to be produced by contractions of single muscle fibers. *Fasciculation* or *fascicular twitching* are preferable terms though it will be pointed out below that the groups of muscle fibers which are involved are much smaller than *fasciculi* in the anatomical sense. Such fasciculations occur most intensely and most characteristically in the various types of progressive degeneration of the motor neurons such as progressive bulbar palsy, progressive spinal muscular atrophy and amyotrophic lateral sclerosis. A typical example is given below:

Case 2. A previously healthy man of 54 years began to notice weakness of the left arm which grew rapidly worse in the next few weeks. About two months after the onset, he found that the right arm was becoming affected in the same manner and later his legs became stiff and his gait awkward. Examination disclosed striking atrophy of the muscles about the shoulders and in the muscles of the arms, above the elbows. The deltoids were most severely affected and the patient could not fully abduct either arm. The affected muscles showed almost constant twitchings. These were best observed in the deltoids over which the skin was very thin. Each twitch seemed to involve a group of muscle fibers about 3 to 5 mm. wide and caused momentarily a shallow groove in the surface of the muscle. Identical twitches occurred in the same group of fibers every few seconds. These twitchings were so numerous in the deltoids that some part of the muscle was always in movement. They were less constant but present in almost all of the muscles of the arms and hands, even in those muscles which showed no atrophy or weakness. The legs were not atrophied but were spastic and weak. A few twitchings were seen in the quadriceps muscles of both legs. The tendon reflexes were increased in the arms and were grossly exaggerated in the legs. Electrical stimulation of the deltoids revealed some reduction of irritability to faradism and also slight slowing of the galvanic response.

During the next few years the disease progressed without interruption. The muscles of the legs became atrophied. Twitchings appeared in the tongue which finally became atrophic and paralysed. Speech and swallowing were impossible and tube feeding was necessary. All the tendon reflexes disappeared. The intercostal muscles were involved and eventually death resulted from exhaustion, failure of respiration and terminal pneumonia some four and a half years after the onset of the malady.

This distressing case is illustrative of this whole group of conditions for the first clinical picture was that of amyotrophic lateral

sclerosis which then passed into progressive bulbar palsy and generalized spinal muscular atrophy. Such terms, of course, indicate merely different varieties of one disease, *i.e.*, progressive degeneration of the motor neurons. The twitchings, it has been taught for many years, indicate a progressive process involving the motor cells lying in the anterior spinal gray matter or corresponding cells lying in the brain stem. Identical, but less constant and less extensive twitchings are found when inflammatory, vascular or neoplastic diseases involve the same cells. As examples, I may mention syringomyelia, gliomas of the spinal cord and syphilitic meningomyelitis.

The essential clinical characteristics of fascicular twitchings were described long ago by Duchenne and others. It is recognized that they involve a very small bundle of muscle fibers and that they are of very brief duration. Any given bundle of fibers may contract at fairly regular intervals, the intervals being, on an average, a few seconds. The contractions of the various bundles in the affected muscle are, of course, not synchronous. Such fasciculations are present when the muscle is completely relaxed but are increased by voluntary contraction of the muscle and also by slapping or pinching the muscle. Minimal contraction of a muscle seems to be the most effective method of provoking the twitchings. When the latter are very active they may cause tremulous movements of the fingers but, as a rule, they are too small to move larger segments of the extremities. Fusion of several fasciculations may, however, give rise to contractions of relatively large parts of a muscle. It is always taught that true fasciculation is invariably associated with progressive atrophy of the affected muscle and therefore is indicative of a progressive process. Since fasciculation is not found in lesions of the nerve roots or of the peripheral nerves, it is believed that its presence indicates involvement of the cell body.

Denny-Brown and Pennybacker have found, in dealing with a particular group of twitching fibers, that the contractions occur at regular intervals varying between 4 and 6 seconds. Each contraction is identical with the previous one as regards both its mechanical and electrical characteristics. Each contraction is associated with a single, diphasic action current. These facts indicate that fasciculation is "a single impulse contraction in a fixed group of muscle fibers."

The authors conclude, therefore, that each contraction represents the discharge of a single motor cell. A motor neuron supplies about 150 muscle fibers, it is estimated, and such a group of fibers is termed a motor unit. Hence, fasciculation may be regarded as a contraction of the muscle fibers innervated by a single motor neuron, or a motor unit. Denny-Brown has shown that the same motor units which take part in spontaneous fasciculation may be induced to contract normally in willed contractions. In fact, voluntary innervation of a muscle enhances fasciculation. The inhibition of a muscle by the voluntary contraction of its antagonist, however, will not stop fasciculation. Shivering, which simulates fasciculation very closely, is associated with a grouped tetanic discharge of action currents and is, therefore, essentially different from fasciculation. These investigators believe that the focus of irritation which produces fasciculation is within the neuron itself. It evidently indicates an abnormality of the neuron but not its destruction for when degeneration has occurred, fasciculation is replaced by fibrillation.

CONTRACTION FASCICULATION

This type of muscular twitching is not recognized by most neurologists and is not properly described, I believe, except in the article by Denny-Brown and Pennybacker already mentioned. I have been interested in this type, however, for several years and have found it most frequently in subjects who have had poliomyelitis many years before and who have shown as a result striking atrophy and weakness of the skeletal muscles. The following case report will serve as an illustration:

Case 3. An elderly man gave a history of an acute illness at the age of 4 years. As a result of this illness he was almost completely paralysed in all four extremities for some months, but eventually improved so as to be able to walk with the help of braces and crutches. His condition remained stationary after this. Examination at the age of 65 years revealed extensive atrophy of the muscles and deformities of the bones. The left leg showed severe but incomplete atrophy about the hip and in the thigh, and almost complete atrophy and paralysis of the calf muscles. The foot was much deformed and fixed in the equinovarus position. The leg was 4 inches shorter than the right and was so much smaller than normal as to resemble that of a child. All muscle groups of the right leg were somewhat atrophic and weak but only the anterior tibial group of muscles

was paralysed. This had resulted in foot drop and contractures. The muscles of the right shoulder girdle and right upper arm were almost completely atrophic. The left arm was not severely affected. The cranial nerves were normal. Sensibility was quite normal. The tendon reflexes were all absent except for the left biceps and triceps. The clinical picture was regarded as quite typical of long standing poliomyelitis. The most interesting feature of the case was the presence of small muscular twitchings in all of the partially atrophied muscles and in some muscles which were not definitely atrophic. These twitchings would appear in great numbers whenever the patient contracted the muscle and were abolished when the muscle was relaxed. Some of them were fine and similar to spontaneous fasciculations but others were much coarser. One gained the impression that the muscle was not contracting as a whole but that large and small groups of fibers were contracting separately. Minimal voluntary contractions of a muscle would make these twitchings most evident and in some instances a maximal contraction would abolish them. The muscles which showed the least atrophy were those in which the twitchings disappeared with strong contractions, whereas the more severely atrophied muscles would usually continue to twitch during a maximal contraction.

The patient has now been under observation for four years and there has been no perceptible change in his condition. The weakness and wasting of his muscles has not progressed.

I have observed such twitchings in 8 cases of poliomyelitis of long standing and also in one case of syphilitic meningomyelitis characterized by severe muscular atrophy (the so-called syphilitic muscular atrophy) in which the progress of the disease had been arrested by antisyphilitic treatment seven years before. Evidently such contraction fasciculations are very common in long standing diseases of the anterior spinal gray matter.[2]

A number of papers may be found in neurological literature dealing with "progressive muscular atrophy" developing years after an attack of acute anterior poliomyelitis. In most of these papers no proof is offered that the disease is actually progressive, and the diagnosis seems to be based upon the presence of fascicular twitchings which

[2] I have never seen contraction fasciculation in patients convalescing from poliomyelitis although I once examined 15 children with this problem in mind. Some of these children had been paralysed for more than a year and some for only a few weeks. I have no explanation to offer for the absence of contraction fasciculation unless one might wish to assume that the fasciculations were concealed by the thickness of subcutaneous fat for all of these children were well nourished and some of them were obese.

are taken to indicate a progressive degeneration of the motor neurons. I am not prepared to say that progressive muscular atrophy never occurs as a late sequel of poliomyelitis, but I can say with confidence that in several cases which I have followed for considerable periods there has been no progression of the atrophy. In the cases in which I have examined the patient only once, the history has always indicated that the condition was stationary. I suspect, therefore, that in most cases in which the diagnosis of progressive muscular atrophy following poliomyelitis has been made, the diagnosis is incorrect and is due to erroneous interpretation of the muscular twitchings. The literature dealing with this subject has been collected recently by Salmon and Riley.

Denny-Brown and Pennybacker state that contraction fasciculation is a series of coarse rhythmical contractions occurring at a rate of 5 to 20 per second. The onset is always at a certain stage of a particular movement. They are most marked in gentle postural contractions and may be obscured in moderate to maximal contractions. They are associated with a rhythmical series of action currents in the muscle which are comparable to those of large motor units in normal muscles. Their explanation for such twitches is essentially as follows: A particular voluntary movement appears to begin always with the contraction of the same motor unit. As the movement continues more and more units enter into contraction in such sequence that the contractions of individual units become fused and the muscle seems to contract as a whole. Under such circumstances the contractions of individual units are obscured. In a muscle wasted by the loss of many motor units, however, this smooth sequence of contraction is interrupted in such a manner as to prevent fusion, and the contractions of individual units become evident. In appearance these contractions are identical with spontaneous fasciculations. Study of the action currents reveals that the active units in such wasted muscles are behaving as they do in normal muscles.

These statements regarding normal muscle may be verified by clinical observation. In a thinly-covered normal muscle illuminated by oblique light one may observe, at the onset of a very gradual minimal contraction, that the contraction begins first in a particular small bundle of muscle fibers and that this is followed at once by

contractions of many other bundles of fibers, which are not exactly synchronous. As the contraction continues the muscle begins to contract as a whole as it does from the outset in stronger and in more abrupt contractions. In my experience, the deltoid muscle is most suitable for this observation.

Contraction fasciculation, therefore, has no such ominous significance as spontaneous fasciculation. It is merely the consequence of loss of a considerable number of motor neurons and may result from nonprogressive processes.

It is of interest to speculate about the anatomical nature of the lesions which cause contraction fasciculation. According to Sherrington most muscles are derived from more than one myotome and receive fibers from more than one segment of the spinal cord. It is believed, however, that each motor root innervates a separate part of such muscles. This statement is obviously true in regard to certain large, flat muscles such as the rectus abdominis, the pectoralis major and the trapezius, for loss of one motor root causes complete paralysis of one part of these muscles and not partial paralysis of the whole muscle. Contraction fasciculation occurs in these muscles when they are partially paralysed as a result of old poliomyelitis but, in my experience, does not occur when the muscle is affected by loss of one motor root. I suspect, therefore, that contraction fasciculation cannot result from section of a spinal root, or a spinal nerve or even from a massive lesion of the spinal gray matter which destroys all the motor cells in any given segment, but must be due to small, disseminated lesions which partially destroy the neurons of one or more segments. Poliomyelitis is, of course, known to cause just such lesions.

BENIGN TWITCHINGS SOMETIMES TERMED MYOKYMIA

Most of us have been annoyed at some time in our lives by small muscular twitchings affecting most commonly the eyelid, which appear and disappear for no apparent reason. Such contractions may persist for a second or more as a sustained spasm, but more commonly occur as a series of briefer twitches. Less commonly similar twitchings are discovered in the hands, forearm, or calves. In my experience, medical students are especially subject to this

complaint. Occasionally one sees a patient, otherwise in good health, who is subject to almost constant twitchings widely distributed throughout the skeletal musculature. There is reason to believe that these generalized twitchings, which have been called *myokymia*, are similar to the more local types mentioned above. The following case record may be offered as illustration:

Case 4. A distinguished physician of middle age had been troubled by muscular twitchings in the arms and legs, and by cramps in the legs for more than 10 years. These varied in intensity but were usually present to some extent. When they were most active the patient was always conscious of them and they might even cause a coarse tremor of the fingers. Fatigue seemed to induce or intensify the twitchings in some instances. The cramps were chiefly in the calves and came on as a rule at night. Examination revealed constant irregular wave-like twitchings, some of which were comparable to fascicular twitches and some of which were larger. In the calf muscles, where they were most evident, they were so numerous as to cause constant movement of the whole surface of the muscle. They were not influenced by voluntary contraction. The muscles were of good bulk and consistency, and their strength was quite normal. The reflexes were all normal and there was no sign of tetany.

Denny-Brown and Pennybacker state that these twitchings are associated with a series of high-frequency electrical discharges lasting from one-twentieth to one-tenth of a second. The mechanical contraction is a slow wave, not a twitch as in fasciculation. The contractions occur in different groups of muscle fibers, independently and intermittently. Successive contractions are irregular in rate, in size and in duration. The irregularity in shape of the successive action currents indicates that we are not dealing with contractions of motor units. Denny-Brown and Pennybacker suggest that the focus of irritation affects unevenly the bundles of nerve fibers within the muscle. They regard this phenomenon as one probably related to vascular cramp or to other change in the vessels which supply the fasciculi, and emphasize the association of the twitchings with muscular cramps. It is mentioned that such twitchings may occur in persons who sweat excessively and who might, therefore, be suspected of sodium chloride deficiency. The administration of sodium chloride, however, is said to be without effect. Calcium is likewise ineffectual in such cases.

Myokymia and related musclar twitchings may be distinguished on clinical grounds from spontaneous fasciculation by the longer duration of the contractions which gives them a slow wave-like effect, and by the absence of associated atrophy of the muscles. Their significance is not known but it is clear that they are of no serious import. They have some undetermined relation to fatigue and to sweating, and are frequently associated with cramps.

CONCLUSIONS

Four types of muscular twitchings have been described and the significance of recent physiological investigations in this field has been emphasized. The essential features of this work may be summarized as follows:

1. True *fibrillations*, *i.e.*, contraction of individual muscle fibers, is a result of complete destruction of the motor neurons and is found in paralysed muscle. The movements are so minute that they can be observed only in thinly covered muscles as, for example, in the tongue, or, rarely, through the intact skin in emaciated individuals.

2. *Spontaneous fasciculation*, often improperly termed fibrillation, is the expression of spontaneous, abnormal discharges of individual motor neurons and indicates progressive degeneration of those neurons. This type of fasciculation is not inhibited by relaxation of the muscle. It is invariably associated with progressive atrophy of the muscle and is characteristic of the various types of progressive spinal muscular atrophy. Spontaneous fasciculation indicates that the motor cells are involved, for lesions in the axons cause fibrillation.

3. *Contraction fasciculation* is a result of loss of motor neurons. The gradual voluntary contraction of a normal muscle is made up of a series of contractions of small groups of muscle fibers, which occur in such sequence that they are fused into a smooth contraction of the whole muscle. The loss of a number of neurons makes this series of contractions discontinuous and prevents proper fusion, and as a result the contractions of individual bundles of fibers become evident. Such fasciculations are present only when the muscle is contracting. They do not necessarily indicate a progressive process.

It is of interest that fibrillation, spontaneous fasciculation and

contraction fasciculation may all be found in amyotrophic lateral sclerosis.

4. *Myokymia* and similar more local muscular twitchings seen most frequently in the eyelids, are distinguished from fasciculation by their longer duration which gives them a wave-like appearance, and by their irregularity in rate and size. They are not associated with weakness or with atrophy of the muscle and have no serious significance. Their origin is discussed above.

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DOES ETHER NARCOSIS PROTECT FROM ANAPHYLACTIC SHOCK?[1]

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For a number of years it has been the general practice in certain hospitals to administer tetanus antitoxin to patients, while under anesthesia, without fear of anaphylactic shock. It has been the belief of the surgeons engaging in this practice that anesthesia in some way removes this danger. This belief has been so fixed that often the usual precautions against anaphylactic shock are not taken before the antitoxin is administered. The anesthesia alone has been considered a sufficient safeguard, and often the preliminary skin test, or ophthalmic test, and the usual questioning as to whether the patient has previously had injections of foreign sera, or has ever shown any allergic symptoms, have been omitted.

We have been interested in this question for a number of years, and have often wondered where the practice originated, and what the scientific basis for it was. Doctor Dean Lewis suggested that the work of Besredka was responsible for it. We looked the matter up, and found that in 1907 Besredka (1) injected guinea-pigs sensitive to horse serum with shocking doses (0.25 cc.) under the dura mater, while under ether anesthesia. There were no signs of anaphylaxis. No mention is made of control animals, and no protocols or other figures are given. It would seem fair to say, therefore, that these experiments were at least not entirely conclusive.

On consulting text-books, we found that Karsner (2) makes the following statement: "Drugs which depress smooth muscle excita-

[1] Read before the Section on Surgery, General and Abdominal, at the Eighty-ninth Annual Session of The American Medical Association, San Francisco, June 17, 1938.

[2] The experiments were carried out in the Bacteriological Laboratory, through the courtesy of Dr. J. Howard Brown.

bility, those which depress nerve activity generally, in the group of narcotics and anesthetics, those which tend to maintain blood pressure, are pharmacologically adapted to the inhibition or even prevention of shock. Thus atropine, adrenalin, chloral hydrate, ether, alcohol, atoxyl, and numerous other drugs have been employed." Manwaring (3) makes the following statement: "Many anesthetics and narcotics act as desensitizing agents. For example, chloral hydrate, chloroform, ethyl chloride and cocaine will completely prevent anaphylactic reactions in guinea-pigs. Ether given in excessive doses will appreciably reduce the anaphylactic susceptibility in these animals." Sherwood (4) states that "... atropine, adrenalin, chloral hydrate, and even ether when administered to guinea-pigs tend to reduce the severity of the symptoms and prevent death in a fairly high percentage of cases." None of these authors refer to the experimental work on which their statements are based. Auer (5), however, states that "Besredka recommended this procedure (ether narcosis), and obtained good results in guinea-pigs. The protective reaction, which is not great, according to other observers, seems to be entirely due to a reduction in irritability of the bronchial muscles."

Having obtained no more than scant and dubious information from text-books, we undertook a more thorough search for original articles. The information obtained, as will be shown in the following paragraphs, was meager, incomplete, and conflicting.

Rosenau and Anderson (6), in 1908, tried Besredka's experiment, and found that seven of eight guinea-pigs died from the effects of the second injection of horse serum. They explain the difference between their results and those of Besredka and Roux, "either by the difference in toxicity of the French and the American serums, or by differences in susceptibility of the animals used." They give no protocols and mention no control experiments.

Banzhaf and Famulener (7), in 1910, reported experiments upon guinea-pigs, from which they concluded that chloral hydrate properly administered would afford protection to sensitized guinea-pigs against shocking doses in practically all cases.

Schultz (8), in 1912, described the anaphylactic response of smooth muscle in guinea-pigs while under ether anesthesia.

Simonds (9), in 1916, found that ether anesthesia did not prevent the fall of blood pressure associated with anaphylactic shock in dogs. Eleven animals were used.

Thomsen (10), in 1917, found that with guinea-pigs weighing between 300 and 400 Gm. ether anesthesia afforded little protection from shock. Using guinea-pigs weighing 800 to 900 Gm., he found a difference in favor of the anesthetized animals. With guinea-pigs weighing 400 to 500 Gm., he also found a difference in favor of the anesthetized animals. However, when more highly sensitized guinea-pigs were used, he found that ether narcosis provided no more protection in the larger animals than in the smaller ones.

Weil (11), also in 1917, reported a series of experiments dealing with anaphylaxis in dogs. He stated that in these animals ether anesthesia did not in the least inhibit acute anaphylactic shock with death. However, he gave no figures, or protocols of experiments, to substantiate his statement.

Kopaczewski, Roffo and Roffo (12), in 1920, stated that intravenous injections of ether protected sensitized guinea-pigs against shock, all the treated animals having survived and all the controls having died. The number of animals used in the experiments was not stated.

Webb (13), in 1924, described the mechanism of anaphylactic leukopenia in dogs under ether anesthesia.

Hanzlik and Stockton (14), in 1927, stated that anesthesia modified the degree of hypertonic contraction in the crop of pigeons in anaphylactic shock, but did not state to what extent the modification took place, nor did they name the anesthetic used, or give protocols of experiments. This was probably because their paper did not deal primarily with the relation of anesthesia to anaphylaxis.

Bally (15), in 1929, gave shocking doses of horse serum to twenty-three sensitized rabbits, while under ether anesthesia. He concluded that the rabbits showed a typical anaphylactic response when under ether anesthesia. Seven of the animals died in shock. He used no controls.

Krafka, McCrea, and Vogt (16), in 1929, studied the anaphylactic reaction of four cats, under urethane anesthesia. The animals were said to be sensitive to shocking doses, but no fatalities were recorded.

Hill and Martin (17), in 1932, made an exhaustive review of all the literature dealing with agents that had been used for the inhibition of anaphylactic shock. They state that:

"There has long been a belief, mainly, we fear, founded on authority, that ether as a narcotic will inhibit shock. Besredka first made the statement. A few other investigators yield confirmatory or contradictory findings. Strangely enough, we can only find one investigator who has thought it advisable to present his protocols. His results are inconclusive."

Scimone (18), in 1934, used rabbits and found that shock occurred in three out of fourteen animals (21 per cent) which had been sensitized under narcosis, while it occurred in six out of eight (75 per cent) control animals. He concludes that narcosis during sensitizing injections protects against shock.

Dragstedt (19), in 1935, stated that "in the dog, my associates and I have used ether, chloroform, paraldehyde, barbital, and vinethene, with and without morphine, and often in combination, without any apparent ameliorating effect [against anaphylaxis]. To be sure, vomiting is prevented in the dog by anesthesia, and perhaps the bronchial constriction in the guinea-pig may be somewhat less intense, but there is no substantial evidence that if sensitization is high the fatal issue has been either postponed or prevented." Dragstedt further refers to evidence that anaphylactic shock is largely is largely a histamine intoxication (20, 21), and that ether anesthesia (22) increases the susceptibility to histamine shock. This, he infers, would lend support to the idea that anesthesia not only would not diminish anaphylactic shock, but would actually increase it.

Re (23), in 1936, reported three sets of experiments using guinea-pigs. The *first group* of animals were sensitized by a subcutaneous injection of 0.5 cc. of horse serum, followed twenty days later by an intracardiac injection of 0.5 cc. of antigen. In this group, which served as control, there were 16 guinea-pigs. Of these, 5 died of shock (31 per cent) while 8 experienced shock but survived (50 per cent), making a total of 13 that displayed anaphylactic phenomena (81 per cent). The *second group* were sensitized while under deep ether narcosis. The shock-provoking injections were given while the animals were conscious. There were 16 animals in this group. Of these, 2 died of shock (12 per cent) while 7 experienced shock but sur-

vived (44 per cent), making a total of 9 that showed anaphylactic phenomena (56 per cent). The animals in the *third group* were sensitized without anesthesia, but the shock-provoking injection was given during ether narcosis. In this group there were 18 animals. Of these, 5 died of shock (27 per cent) while 4 experienced shock but survived (23 per cent), making a total of 9 that displayed anaphylactic phenomena (50 per cent).

Comparative study of the results in Re's three groups of animals showed that there actually existed a certain degree of protection when the sensitizing or provoking injections were made during narcosis. Thus, while the percentage of control animals presenting the typical symptoms of anaphylactic shock was eighty-one, it was fifty-six for those animals which received a sensitizing injection while they were under anesthesia, and fifty for the animals which received shock-provoking injections during narcosis. In this latter group, however, it was noted that while the percentage of anaphylactic symptoms was lower than in the first two groups, the protection was only relative because the percentage of animals which presented a fatal shock was twenty-seven, almost equalling that in the first group in which it was thirty-one, while in the second group the percentage of fatal shock was only twelve.

Quill (24), last year (1937), contributed what is probably the most pertinent paper that has yet been published on this subject. He reported the case of a man who died, apparently of anaphylactic shock, following the administration of tetanus antitoxin, while under ether anesthesia, at the end of an operation for a gunshot wound of the abdomen. (The interpretation of the case is not clear-cut, for the man had also received a blood transfusion.) This is the only case of its kind that we have found in the literature, although Quill states that a probable instance of anaphylaxis in man, during ether anesthesia, has been observed at another clinic besides that from which he reported his case.

The case reported by Quill stimulated him to undertake experiments on dogs, guinea-pigs, and rabbits. He found that fatal reactions occurred during ether anesthesia in 3 out of 6 dogs, in 5 out of 5 guinea-pigs, and in 5 out of 5 rabbits. He states that there was a violent anaphylactic reaction in the dogs that survived.

We could find in the literature no other account of experimental

work done on this subject. The results obtained in the work that has has been done, are conflicting and inconclusive, and often have no direct bearing upon the present problem.

In the Spring of 1935, Doctor J. Howard Brown was good enough to sensitize two guinea-pigs for us with horse serum (0.5 cc. each, intraperitoneally). After they had become sensitive, we anesthetized one with ether and injected it intraperitoneally with 1 cc. of horse serum. The other animal was similarly injected without anesthesia. Within a short time the unanesthetized animal showed definite symptoms of anaphylactic shock, as manifested by its repeatedly rubbing its nose, and by twitchings and localized convulsions while the animal lay on its side. This control animal died about two hours after the injection. The anesthetized animal showed mild symptoms of anaphylaxis, but recovered.

In November 1935, Doctors Earl L. Burky and Leslie N. Gay became interested in the subject and did a few experiments for their own satisfaction, without any intention of publishing their results. They have kindly furnished us with their experimental data, and have given us permission to include their experiments in this paper. On November 18, 1935, they gave five guinea-pigs sensitizing doses of 1 cc. each of horse serum intraperitoneally. Shock-provoking doses were administered on December 9th, as follows: Guinea-pig no. 1 was injected intravenously with 0.8 cc. of equal parts of horse serum and Ringer's Solution, under ether anesthesia. The injection was given as soon as the anesthesia was profound, the anesthetic being continued for 15 minutes thereafter. No. 2 was injected in the same manner as no. 1, except that the anesthetic was continued for only 10 minutes after the injection. Both these animals survived. Nos. 3 and 4 were injected exactly as nos. 1 and 2, but without anesthesia. One died in $3\frac{1}{2}$ minutes, and one in 4 minutes. No. 5 was injected, without anesthesia, with 0.8 cc. of equal parts of horse serum and adrenalin. This animal survived.

With these leads, we proceeded to carry out a more extensive series of experiments in order further to determine the influence of anesthesia on the anaphylactic reaction. Accordingly, on December 21, 1935 we injected twenty-four guinea-pigs (weighing approximately 300 Gm. each) intramuscularly with 0.25 cc. each of human serum, so as to

have a supply of sensitized guinea-pigs for our experiments. The following is a record of the experiments performed:

Jan. 11, 1936: Two sensitized guinea-pigs, anesthetized with ether, were each injected intramuscularly with 1 cc. of human serum. Two sensitized controls were similarly injected without anesthesia. All animals were observed for three-quarters of an hour following injection. Both unanesthetized animals showed evidence of anaphylaxis, as manifested by persistent rubbing of the nose, and one of them had marked diarrhea. One of the anesthetized animals showed an asthmatic type of breathing which may have been due to the anesthetic. All these animals were still alive and well two days later.

Jan. 13, 1936: Under ether anesthesia each of two sensitized guinea-pigs was injected with 2 cc. of human serum intraperitoneally. Two sensitized controls were similarly injected without anesthesia. All animals were observed for three-quarters of an hour following injection. The anesthetized animals showed no signs of anaphylaxis, except that one of them rubbed its nose a few times. Both unanesthetized animals showed marked symptoms of anaphylaxis, as manifested by rubbing of the nose, staggering gait, lying on the side, and labored breathing. At the end of two hours, the animals were again observed in their cage, and one of the unanesthetized animals was dead, but apparently had been dead only a short time. Autopsy showed some redness of the peritoneum, but no perforation of the bowel, or peritonitis. The lungs were not inflated, but were normal in appearance.

Jan. 14, 1936: Four sensitized guinea-pigs were etherized and each was injected with 3 cc. of human serum intraperitoneally. Four sensitized control, unanesthetized guinea-pigs were similarly injected. The animals were observed for three-quarters of an hour, and the anesthetized animals showed no anaphylactic symptoms. All four unanesthetized animals showed symptoms consisting of persistent rubbing of the nose, muscular twitchings and spasms, staggering gait, inability properly to control the hind quarters, and labored breathing. The breathing of these four animals was distinctly audible, as though there were fluid in the lungs. None of the animals died during the observation period. Two of them looked as if they might die within a short time. Two hours after injection the animals were observed in their cage, and one of the unanesthetized group was found dead. Autopsy showed no perforation of the gut. The peritoneum was slightly red. The lungs were inflated, entirely filling the chest cavity.

Jan. 15, 1936: Two sensitized guinea-pigs were etherized and each was injected with 5 cc. of human serum intraperitoneally. Two sensitized controls were similarly injected without anesthesia. Within 5 minutes the two unanesthetized animals began to show symptoms of anaphylaxis. These symptoms continued during the 45-minute period of observation, and consisted of rubbing of the nose, sneezing, dragging of the hind-quarters, labored and audible respiration. Both animals looked very sick. The anesthetized animals showed no symptoms, except

that one rubbed his nose a few times, and the other showed somewhat labored, but not audible breathing. The animals were observed in their cage three hours after injection, and one of the unanesthetized animals was found dead. It had evidently been dead for some time. Autopsy showed the peritoneal cavity to be normal, except for slight redness. The lungs were not inflated.

To *summarize* this series of experiments, twenty guinea-pigs sensitive to human serum were injected with shock-producing doses of serum. Half of these animals were injected while under ether anesthesia and half without anesthesia. All of the unanesthetized animals showed marked symptoms of anaphylaxis, and three of them (30%) died. Seven of the anesthetized animals showed no symptoms of anaphylaxis whatsoever, three had mild symptoms, and none died.

The anesthetized animals were injected as soon as it was considered that they were under relatively deep anesthesia, that is, when they showed absence of eyelid reflexes and when their limbs became fairly limp. As soon as this stage was reached, the asministration of the anesthetic was discontinued and the animals were injected. No more anesthetic was given after the injection. No effort was made to determine the effect of various degrees of anesthesia, or of prolonging the anesthetic for varying periods of time.

Feb. 19, 1936: Seven of the guinea-pigs that had survived the preceding series of experiments were injected intracardially each with 1 cc. of human serum, four while under ether anesthesia and three without anesthesia, as follows:

No. 1. Injected under very light anesthesia. Dead in three minutes. Autopsy showed no intrapercardial hemorrhage. Lungs inflated.

No. 2. Injected without anesthesia. Immediately showed symptoms of anaphylaxis—rubbing nose, staggering gait, labored breathing, looked sick and as if it were going to die. Better in an hour. Survived. Died 2¼ days later. Not autopsied.

No. 3. Injected under profound anesthesia. Died five minutes after injection. Autopsy showed no intrapericardial hemorrhage. Lungs not inflated.

No. 4. Injected under profound anesthesia. Died five minutes after injection. Autopsy showed small intrapericardial hemorrhage, but not enough to embarrass cardiac action. Lungs not inflated.

No. 5. Injected without anesthesia. Showed same symptoms as no. 2. Better in an hour. Survived.

No. 6. Injected without anesthesia. Died two minutes after injection. Autopsy showed no intrapericardial hemorrhage. Lungs not inflated.

No. 7. Injected under profound ether anesthesia. Died ten minutes after injection. Autopsy showed no intrapericardial hemorrhage. Lungs not inflated.

In *summary*, 7 guinea-pigs sensitive to human serum were injected with shock-producing doses of serum, 4 under ether anesthesia, and 3 without anesthesia. All four of the anesthetized animals died promptly. One of the three animals injected without anesthesia died, and two survived.

These experiments, using the intracardial method of injection, were so at variance in their results from the other experiments we had conducted that we

decided to abandon the method, feeling (though we could not prove it) that there was probably some mechanical factor involved, which might in some way vitiate our results.

Feb. 25, 1936: A new batch of guinea-pigs (weighing approximately 300 Gm. each) were given sensitizing injections. Twelve were given 1 cc. each of horse serum, intraperitoneally. Twelve more were injected with 2 cc. each of equal parts of egg albumen and normal salt solution intraperitoneally. These were used in the following experiments:

March 18, 1936: Eight guinea-pigs sensitive to egg albumen were injected intraperitoneally with 12 cc. each of equal parts egg albumen and normal salt solution, 4 while under ether anesthesia and 4 without anesthesia. The anesthetized animals were injected as soon as the anesthesia was profound, and the deep anesthesia was continued for one minute after injection, following which the animals were allowed to wake up. The following are the protocols:

No. 1. Without anesthesia. Injected 10:42 A.M. No symptoms except nervous overactivity. Animal survived.

No. 2. Ether anesthesia. Injected 10:46 A.M. No symptoms except those attributable to the anesthetic. Survived.

No. 3. Without anesthesia. Injected 10:54 A.M. Sneezing in about one minute. Convulsions 11 A.M. Died 11:06 A.M. *Autopsy:* Abdomen normal. Lungs inflated.

No. 4 Ether anesthesia. Injected 10:50 A.M. No symptoms except those attributable to the anesthetic. Survived.

No. 5. Without anesthesia. Injected 11:06 A.M. Convulsions 11:34 A.M. Died 11:38 A.M. *Autopsy:* Abdomen normal. Lungs inflated.

No. 6. Ether anesthesia. Injected 11:11 A.M. Died 11:21 A.M., without showing any special symptoms except those from the anesthetic. *Autopsy:* Abdomen normal. Right lung inflated. Left lung small, hemorrhagic and consolidated. Sections showed pneumonia.

No. 7. Without anesthesia. Injected 11:15 A.M. Convulsions 11:30 A.M. Died 11:34 A.M. *Autopsy:* Abdomen normal. Lungs inflated.

No. 8. Ether anesthesia. Injected 11:19 A.M. No symptoms except those attributable to the anesthetic. Survived.

Summary. In this experiment 8 animals sensitive to egg albumen were given injections of shock-provoking doses, 4 without anesthesia and 4 under ether anesthesia. Of the four injected without anesthesia, three died. Of the four injected under anesthesia one died, and at autopsy this animal was found to have pneumonia, which was undoubtedly a large contributing factor in its death.

March 21, 1936: Eight guinea-pigs sensitive to horse serum were injected intraperitoneally, each with 6 cc. of horse serum, 4 while under ether anesthesia, and 4 without anesthesia. In the case of the anesthetized animals, injection was made as soon as the anesthesia was profound, and the administration of the anesthetic was continued for one minute after injection. None of the anesthetized animals showed any symptoms whatsoever of anaphylaxis. One of the unanesthetized

ones showed convulsions soon after injection, which persisted for about an hour. Another had its hind legs paralyzed for half an hour or so. All animals in the series survived.

April 11, 1936: Six of the guinea-pigs that survived the experiments of March 21st, and, therefore, presumably had now again become sensitive to horse serum, were injected each with 2 cc. of horse serum *via* the thigh vein, 3 under ether anesthesia and 3 without anesthesia, as follows:

No. 1. Without anesthesia. Injected 9:30 A.M. Only about half of the serum entered the vein, the rest escaped into subcutaneous tissue. Sneezing, staggering, and roughened coat ensued within five minutes. Survived.

No. 2. Without anesthesia. Injected 9:50 A.M. Convulsions immediately. Died 9:58 A.M. *Autopsy:* Lungs inflated.

No. 3. Ether anesthesia. Injected 10:05 A.M., only about half of the serum going into the vein. No symptoms. Survived.

No. 4. Ether anesthesia. Injected 10:20 A.M. No symptoms. Survived.

No. 5. Without anesthesia. Injected 10:30 A.M. Convulsions immediately. Survived.

No. 6. Ether anesthesia. Anesthesia too deep. Died from the anesthetic before injection.

Summary. Five animals sensitive to horse serum were given injections of shock-provoking doses, 3 without anesthesia and 2 under ether anesthesia. Of the three injected without anesthesia, all showed symptoms of anaphylaxis and one died. The two injected while under ether anesthesia showed no symptoms and both survived.

April 23, 1936: Twenty-four large-sized guinea-pigs averaging about 650 Gm., but varying from 450 to 1000 Gm., were given sensitizing doses of 1 cc. of horse serum intraperitoneally.

May 16, 1936: Eight guinea-pigs that were sensitized on April 23rd were injected with 2 cc. each of horse serum *via* the jugular vein, as follows:

No. 1. Without anesthesia. Injected 9:35 A.M. Severe convulsions immediately, from which the animal recovered in a few minutes.

No. 2. Without anesthesia. Injected 9:44 A.M. Very severe convulsions and opisthotonus immediately. The animal recovered in about ten minutes.

No. 3. Without anesthesia. Injected 9:55 A.M. Very severe convulsions immediately. Died three minutes after injection. *Autopsy:* Lungs not inflated.

No. 4. Without anesthesia. Injected 10:11 A.M. Very severe convulsions immediately, but recovered in about ten minutes.

No. 5. Ether anesthesia started at 10:15 A.M. Injected 10:40 A.M. Ether discontinued 10:48 A.M. No symptoms.

No. 6. Ether started 10:47 A.M. Injected 11:09 A.M. Ether discontinued 11:11 A.M. No symptoms.

No. 7. Ether started 11:12 A.M. Injected 11:22 A.M. Ether discontinued 11:25 A.M. No symptoms.

No. 8. Ether started 11:27 A.M. Injected 11:36 A.M. Animal showed no

symptoms following injection, but seemed under light anesthesia. The anesthesia was then increased until the animal was under profound anesthesia. At this point the animal was moved from the table to the floor, the breathing being very shallow. A minute or two later, it stopped breathing and could not be resuscitated. However, it showed no convulsions or other symptoms. *Autopsy:* Showed the lungs not to be inflated.

Summary. Four animals sensitive to horse serum were given shock provoking doses without anesthesia, and four while under ether anesthesia. Of the four injected without anesthesia, all had severe convulsions and one died. Of the four injected while under anesthesia, none showed any symptoms of anaphylaxis, and one died, obviously as a result of forcing the anesthesia too far after injection.

May 19, 1936: Eleven guinea-pigs that were sensitized on April 23rd were injected with 2 cc. each of horse serum *via* the jugular vein, as follows:

No. 1. Without anesthesia. Injected 9:07 A.M. Severe convulsions started immediately. Died 9:12 A.M. *Autopsy:* Lungs inflated.

No. 2. Without anesthesia. Injected 9:15 A.M. Convulsions immediately, from which the animal recovered in a few minutes.

No. 3. Without anesthesia. Injected 9:23 A.M. Severe convulsions started immediately, followed by incontinence. Died 9:28 A.M. *Autopsy:* Lungs inflated.

No. 4. Without anesthesia. Injected 9:34 A.M. Severe convulsions imimmediately, followed by paralysis of hind legs. Recovered in about ten minutes.

No. 5. Ether started 9:36 A.M. Injected 9:43 A.M. Ether discontinued at 9:45 A.M. Animal showed no symptoms.

No. 6. Ether started 9:47 A.M. Anesthesia became so deep that artificial respiration had to be resorted to. When animal began breathing regularly again, it was injected at 10:05 A.M. A little more ether was administered, but was discontinued at 10:06 A.M. Animal showed no symptoms.

No. 7. Ether started 10:08 A.M. Injected 10:24 A.M. Ether discontinued at time of injection. Anesthesia was very light at this time. No symptoms.

No. 8. Ether started 10:27 A.M. Injected 10:35 A.M. Anesthesia was very light and the animal was blinking its eyes and moving its legs as soon as released from the board after injection. Ether was, therefore, started again, but the anesthesia became very deep and the ether was discontinued about one minute after injection. Animal died at 10:38, presumably from the effects of the anesthetic. *Autopsy:* Lungs not inflated.

No. 9. Ether started 10:40 A.M. Injected 10:46 A.M. Ether discontinued just before injection. No symptoms.

No. 10. Ether started 10:50 A.M. Injected 10:58 A.M. Ether discontinued just before injection. No symptoms.

No. 11. Without anesthesia. Injected 11:10 A.M. Convulsions immediately, from which it recovered in a few minutes.

Summary. Eleven animals sensitive to horse serum were given shock provoking doses, 5 without anesthesia and 6 while under ether anesthesia. Of the five

injected without anesthesia, all had severe convulsions and two died. Of the six injected while under anesthesia, none showed any symptoms of anaphylaxis. However, one of these animals died, presumably from the effects of the anesthetic.

June 16, 1936: Twenty-three guinea-pigs, none weighing less than 700 Gm., injected subcutaneously with a sensitizing dose of 0.5 cc. of horse serum in the right thigh.

July 11, 1936: Only nine of the twenty-three guinea-pigs injected on June 16th survived. These nine were injected, each with 2 cc. of horse serum intravenously, except no. 6, who was given 3 cc. The following are the individual records:

No. 1. Without anesthesia. Injected 9:10 A.M. Convulsions immediately. Incontinence of urine one minute after injection. Recovered.

No. 2. Without anesthesia. Injected 9:17 A.M. Convulsions immediately. Recovered.

No. 3. Without anesthesia. Injected 9:25 A.M. Convulsions immediately. The latter subsided, but animal looked very sick and died at 10 A.M., with froth exuding from nostrils. *Autopsy:* Was not done until an hour later, at which time the lungs were collapsed.

No. 4. Without anesthesia. Injected 9:31 A.M. Convulsions immediately. Died 9:35 A.M. *Autopsy:* Lungs inflated.

No. 5. Without anesthesia. Injected 9:40 A.M. Convulsions immediately. Recovered.

No. 6. Without anesthesia. Injected 9:50 A.M. Convulsions immediately. Recovered.

No. 7. Ether started at 10:02 A.M. Discontinued at 10:05 A.M. Injected 10:05 A.M. No symptoms. Animal recovered from the anesthetic sufficiently to get up at 10:08 A.M.

No. 8. Ether started at 10:12 A.M. Discontinued at 10:17 A.M. Animal injected 10:17 A.M. No symptoms. Up at 10:34 A.M.

No. 9. Ether started at 10:22 A.M. Discontinued at 10:30 A.M. Injected at 10:30 A.M. No symptoms. Up at 10:42 A.M.

Summary. Nine animals sensitive to horse serum were given shock provoking doses, 6 without anesthesia and 3 while under ether anesthesia. All of the six injected without anesthesia had severe convulsions and two of them died. None of the three injected while under anesthesia showed any symptoms of anaphylaxis and none died.

Sept. 2, 1936: Eight guinea-pigs, all of which had been used in previous experiments, were injected, each with 2 cc. of horse serum intravenously. Four were injected without anesthesia and four while under ether anesthesia, as follows:

No. 1. Without anesthesia. Injected 9:57 A.M. Convulsions immediately. Died 10:02 A.M. *Autopsy:* Lungs inflated.

No. 2. Without anesthesia. Injected 10:07 A.M. Convulsons immediately. Died 10:14 A.M. *Autopsy:* Lungs inflated.

No. 3. Without anesthesia. Injected 10:16 A.M. Convulsions immediately. Died 10:20 A.M. *Autopsy:* Lungs inflated.

No. 4. Without anesthesia. Injected 10:24 A.M. Convulsions immediately. Died 10:30 A.M. *Autopsy:* Lungs inflated.

No. 5. Ether started 10:33 A.M. Injected 10:46 A.M. Ether discontinued just before injection. No reaction. Up at 11:10 A.M.

No. 6. Ether started 10:55 A.M. Ether discontinued 11:06 A.M. Injected 11:06 A.M. No reaction. Up at 11:30 A.M.

No. 7. Ether started 11:12 A.M. Discontinued 11:21 A.M. Injected 11:21 A.M. No reaction. Up at 11:30 A.M.

No. 8. Ether started 11:26 A.M. Animal breathing in very shallow fashion. Thought to be dead once or twice. Ether discontinued 11:36 A.M. Injected 11:36 A.M. Animal stiffened immediately after injection, but had no convulsions. Was up at 11:38 A.M. Died 11:40 A.M., without convulsions. *Autopsy:* Showed the left lung to be normal in appearance, and not inflated. The entire right lung was atelectatic and the upper lobe was densely adherent to the posterior thoracic wall.

Summary. Eight animals sensitive to horse serum were given shock producing doses, 4 without anesthesia and 4 while under ether anesthesia. All of the four injected without anesthesia had convulsions and died. Of the four injected while under anesthesia, none showed any symptoms of anaphylaxis; one died, probably as the result of a pathological conditon of the right lung.

Aug. 3, 1937: Sixty-three guinea-pigs, none weighing less than 650 grams, injected subcutaneously with a sensitizing dose of 1 cc. of horse serum each, in the right thigh.

Aug. 28, 1937: Twelve guinea-pigs that were sensitized on Aug. 3rd were injected, each with 2 cc. of horse serum intravenously, 8 without anesthesia, and 4 while under ether anesthesia, as follows:

No. 1. Without anesthesia. Injected 4:36 P.M. Convulsions 4:38 P.M. Died 4:40 P.M. *Autopsy:* Lungs inflated.

No. 2. Without anesthesia. Injected 4:46 P.M. Recovered.

No. 3. Without anesthesia. Injected 4:59 P.M. Asthmatic breathing. Left laboratory at 6:10 P.M. Animal very sick. Returned at 8:30 P.M. to find animal dead and stiff. *Autopsy:* Lungs not inflated.

No. 4. Without anesthesia. Injected 5:22 P.M. Recovered.

No. 5. Without anesthesia. Injected 5:27 P.M. Recovered.

No. 6. Without anesthesia. Injected 5:39 P.M. Recovered.

No. 7. Without anesthesia. Injected 5:48 P.M. Recovered.

No. 8. Without anesthesia. Injected 6:02 P.M. Left laboratory at 6:10 P.M. Returned at 8:30 P.M. Animal dead and stiff. *Autopsy:* Lungs not inflated.

No. 9. Ether started at 8:45 P.M. Injected 8:52 P.M. Up at 10:13 P.M. Recovered with no reaction.

No. 10. Ether started at 8:55 P.M. Injected at 9:08 P.M. Up at 9:11 P.M. Recovered without reaction.

No. 11. Ether started at 9:30 P.M. Injected 9:40 P.M. Up immediately. Recovered without reaction.

No. 12. Ether started at 9:56 P.M. Injected at 10:11 P.M. Breathing normally at 10:31 P.M., when we left the laboratory. Recovered.

Summary. Twelve animals sensitive to horse serum were given shock producing doses, 8 without anesthesia, and 4 while under ether anesthesia. Three of the eight injected without anesthesia died. None of those injected while under anesthesia died.

Sept. 11, 1937: Five animals that were sensitized on August 3rd, were injected each with 2 cc. of horse serum intravenously, 4 while under ether anesthesia and 1 without anesthesia, as follows:

No. 13. Ether started at 2:44 P.M. Injected 2:52 P.M. Up at 2:59 P.M. Recovered, without reaction.

No. 14. Ether started at 2:55 P.M. Injected at 3:01 P.M. Up immediately. Convulsions 3:04 P.M. Died 3:09 P.M. *Autopsy:* Lungs inflated.

No. 15. Ether started at 3:07 P.M. Injected 3:18 P.M. Up at 3:29 P.M. Recovered without reaction.

No. 16. Ether started at 3:20 P.M. Injected at 3:28 P.M. Up at 3:30 P.M. Recovered, without reaction.

No. 17. Without anesthesia. Injected 3:38 P.M. Recovered.

Summary. Five guinea-pigs sensitive to horse serum were injected with shock-producing doses, 4 while under ether anesthesia, and one without anesthesia. One of the four injected while under anesthesia died, and three recovered. The one injected without anesthesia recovered.

October 2, 1937: Five animals that were sensitized on August 3rd, were injected each with 2 cc. of horse serum intravenously, 3 while under anesthesia and 2 without anesthesia, as follows:

No. 18. Ether started at 8:57 A.M. The anesthetic induced frothing from the nose before injection. Injected at 9:03 A.M. Died at 9:07 A.M., without convulsions. *Autopsy:* Lungs inflated.

No. 19. Ether started at 9:07 A.M. The anesthetic induced frothing from the nose before injection. Injected 9:29 A.M. Minor convulsion 9:31 A.M. Died 9:34 A.M. *Autopsy:* Lungs inflated.

No. 20. Without anesthesia. Injected 9:38 A.M. Convulsions 9:41 A.M. Died 9:43 A.M. *Autopsy:* Lungs inflated.

No. 21. Without anesthesia. Injected 9:48 A.M. No reaction whatsoever. Recovered.

No. 22. Ether started 9:51 A.M. Injected 9:57 A.M. Died 9:59 A.M., without convulsions. *Autopsy:* Lungs inflated.

Summary. Five guinea-pigs sensitive to horse serum were injected with shock-producing doses, three while under ether anesthesia, and two without anesthesia. All three of those injected while under ether anesthesia died. One injected without anesthesia died, and one recovered.

Jan. 20, 1938: Thirty guinea-pigs, none weighing less than 650 Gm., were

injected subcutaneously, with a sensitizing dose of 1 cc. of horse serum each in the right thigh.

March 3, 1938: Eleven animals that were sensitized on Jan. 20th were injected each with 2 cc. of horse serum intravenously, 6 while under ether anesthesia and 5 without anesthesia. In the anesthetized animals, the injection in each case was made as soon as good surgical anesthesia was obtained, and the anesthesia was discontinued as soon as the injection was made. The records were as follows:

No. 1. Without anesthesia. Injected 9:28 A.M. Asthmatic breathing started at once. Died 10:20 A.M. *Autopsy:* Lungs not inflated.

No. 2. Ether started 9:38 A.M. Injected 9:43 A.M. Up at 10:25 A.M. Recovered. No symptoms of anaphylaxis.

No. 3. Without anesthesia. Injected 9:52 A.M. Convulsions 9:56 A.M. Died 12:15 P.M., after we had left the laboratory. No autopsy.

No. 4. Ether started 9:55 A.M. Injected 10:05 A.M. Up 10:25 A.M. Recovered without any symptoms of anaphylaxis.

No. 5. Without anesthesia. Injected 10:10 A.M. Convulsions immediately, but animal recovered.

No. 6. Ether started 10:15 A.M. Injected 10:26 A.M. Up 10:48 A.M. Recovered without symptoms of anaphylaxis.

No. 7. Without anesthesia. Injected 10:38 A.M. Convulsions immediately, but animal recovered.

No. 8. Ether started at 10:40 A.M. Injected 10:45 A.M. Up 10:48 A.M. Recovered without symptoms of anaphylaxis.

No. 9. Without anesthesia. Injected 10:55 A.M. Convulsions 10:57 A.M. Died 10:59 A.M. *Autopsy:* Lungs inflated.

No. 10. Ether started 10:57 A.M. Injected 11:06 A.M. Up 11:10 A.M. Recovered without symptoms of anaphylaxis.

No. 11. Ether started 11:12 A.M. Injected 11:20 A.M. Put back in cage before it had gotten up. Had not reacted when we left the laboratory. Animal recovered.

Summary. Eleven guinea-pigs sensitive to horse serum were injected with shock-producing doses, six while under ether anesthesia, and five without anesthesia. All six of those injected while under anesthesia recovered. Three of the five injected without anesthesia died.

March 5, 1938: In order to get an estimate of the incidence of ether deaths when surgical anesthesia was induced in guinea-pigs, we decided to induce surgical anesthesia in all the guinea-pigs we had on hand, without doing anything else to them, to see if there were any ether deaths. This was done as a control experiment, to compare these animals with those that were given a shocking dose of horse serum during anesthesia. There were seventeen guinea-pigs in all. Each of them was anesthetized until surgical anesthesia was produced, and was then kept under surgical anesthesia for five minutes. Four groups of guinea-pigs were used, as follows:

Group I. There were six guinea-pigs in this group, all of which had been given

shocking doses of horse serum on March 3rd, while under ether anesthesia, and all of which had recovered. The following are the records:

No. 1. Ether started 9:43 A.M. Discontinued 9:49 A.M. Up 9:54 A.M.
No. 2. Ether started 9:51 A.M. Discontinued 9:57 A.M. Up 10:26 A.M.
No. 3. Ether started 9:58 A.M. Discontinued 10:05 A.M. Up 10:18 A.M.
No. 4. Ether started 10:06 A.M. Discontinued 10:12 A.M. Up 10:25 A.M.
No. 5. Ether started 10:12 A.M. Discontinued 10:18 A.M. Up 10:25 A.M.
No. 6. Ether started 10:19 A.M. Discontinued 10:25 A.M. Up 10:35 A.M.

Group II. This group included only two guinea-pigs which had recovered from shocking doses of horse serum given on March 3, 1938, without anesthesia. The following are the records:

No. 1. Ether started 11:23 A.M. Discontinued 11:28 A.M. Up 11:40 A.M.
No. 2. Ether started 11:29 A.M. Discontinued 11:35 A.M. Up 11:55 A.M.

Group III. This group included two animals that had recovered from shocking doses of horse serum on October 2, 1937. The record of each follows:

No. 1. Ether started 11:35 A.M. Discontinued 11:40 A.M. Up 11:58 A.M.
No. 2. Ether started 11:41 A.M. Discontinued 11:47 A.M. Up 12:03 A.M.

Group IV. This group included seven guinea-pigs that had never been sensitized to horse serum and had never been etherized before. The record of each follows:

No. 1. Ether started 10:31 A.M. Discontinued 10:37 A.M. Up 10:46 A.M.
No. 2. Ether started 10:38 A.M. Discontinued 10:44 A.M. Up 10:57 A.M.
No. 3. Ether started 10:45 A.M. Discontinued 10:56 A.M. Up 11:11 A.M.
No. 4. Ether started 10:46 A.M. Discontinued 10:57 A.M. Up 11:04 A.M.
No. 5. Ether started 10:58 A.M. Discontinued 11:04 A.M. Up 11:22 A.M.
No. 6. Ether started 11:05 A.M. Discontinued 11:11 A.M. Up 11:20 A.M.
No. 7. Ether started 11:12 A.M. Discontinued 11:18 A.M. Up 11:23 A.M.

All seventeen animals in these control experiments, using surgical anesthesia alone, recovered.

Mar. 19, 1938: Six guinea-pigs, none weighing less than 650 Gm., were injected subcutaneously, with a sensitizing dose of 1 cc. of horse serum each.

April 23, 1938: Five guinea-pigs that were sensitized on Mar. 19th were injected each with 2 cc.[3] of horse serum intravenously, 2 while under ether anesthesia, and 3 without anesthesia. In the anesthetized animals, the injection in each case was made as soon as good surgical anesthesia was obtained, and the anesthesia was discontinued as soon as the injection was made. The sixth guinea-pig sensitized on Mar. 19th was anesthetized, but died under the anesthetic before the serum could be injected. The records follow:

No. 1. Without anesthesia. Injected 9:27 A.M. Became rigid immediately. Died 9:33 A.M. Autopsy not done.

No. 2. Ether started 9:30 A.M. Injected 9:42 A.M. Up at 9:54 A.M. Recovered. No symptoms of anaphylaxis.

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[3] This had gradually come to be considered the optimum shocking dose.

No. 3. Without anesthesia. Injected 9:47 A.M. Convulsions immediately. Died 9:52 A.M. No autopsy.

No. 4. Ether started 9:48 A.M. Injected 9:55 A.M. Up at 9:59 A.M. Recovered. No symptoms of anaphylaxis.

No. 5. Without anesthesia. Injected 10:01 A.M. Recovered.

No. 6. Ether started 10:04 A.M. Died 10:06 A.M., before injection could be made.

Two animals that were sensitized on Aug. 3, 1937 and given shocking doses on Oct. 2, 1937 were injected (April 23) just as the foregoing series were, one while under ether anesthesia, and one without anesthesia. The records follow:

No. 1. Ether started 10:10 A.M. Injected 10:18 A.M. Died 10:27 A.M. No autopsy.

No. 2. Without anesthesia. Injected 10:23 A.M. Convulsions immediately. Died 10:30 A.M. No autopsy.

Five animals that were sensitized on Jan. 20, 1938 and given shocking doses on Mar. 3, 1938, from which they recovered, were injected (April 23) just as the others were, 2 while under ether anesthesia, and 3 without anesthesia. The first of the series had been given its shocking dose without anesthesia on Mar. 3rd, and the other four had had shocking doses while under ether anesthesia. The records follow:

No. 1. Without anesthesia. Injected 10:36 A.M. Only slight symptoms at first, but died at 11:22 A.M. No autopsy.

No. 2. Ether started 10:38 A.M. Injected 10:47 A.M. Died 10:53 A.M. No symptoms of anaphylaxis. No autopsy.

No. 3. Without anesthesia. Injected 10:53 A.M. Convulsions immediately. Died 10:57 A.M. No autopsy.

No. 4. Ether started 10:55 A.M. Injected 11:03 A.M. Died 11:07 A.M. No symptoms of anaphylaxis. No autopsy.

No. 5. Without anesthesia. Injected 11:08 A.M. Symptoms of anaphylaxis not striking, but died at 11:15 A.M.

Summary. Twelve guinea-pigs sensitive to horse serum were given injections of shock producing doses, five while under ether anesthesia, and seven without anesthesia. Of the five injected while under anesthesia, three died. Of the seven injected without anesthesia, six died.

SUMMARY

Table 1 gives a general summary of the results. Sixty-nine guinea-pigs sensitive to foreign protein were given shock-provoking doses without anesthesia. Thirty-six (52.2 per cent) lived and thirty-three (47.8 per cent) died. Sixty-five guinea-pigs sensitive to foreign protein were given shock-provoking doses while under ether anesthesia. Fifty (76.9 per cent) of these lived and fifteen (23.1 per cent) died.

Of the fifteen that died, one had pneumonia when injected, and another a completely atelectatic lung, as shown by autopsy. A third died because the anesthesia was forced too far. A fourth death was probably due to the anesthesia. In the two animals that had pneumonia

TABLE 1

Summary of results

Animals sensitive to foreign protein were injected with shocking doses, some while under ether anesthesia and some without anesthesia.

EXPERIMENT	SITE OF INJECTION	NO. ANIMALS INJECTED	ANESTHESIA		NO ANESTHESIA	
			Lived	Died	Lived	Died
1	Per Cav.	2	1	0	0	1
2	Vein	4	2	0	0	2
3	Muscle	4	2	0	2	0
4	Per Cav.	4	2	0	1	1
5	Per Cav.	8	4	0	3	1
6	Per Cav.	4	2	0	1	1
7	Heart	7	0	4	2	1
8	Per Cav.	8	3	1*	1	3
9	Per Cav.	8	4	0	4	0
10	Vein	5	2	0	2	1
11	Vein	8	3	1†	3	1
12	Vein	11	5	1‡	3	2
13	Vein	9	3	0	4	2
14	Vein	8	3	1§	0	4
15	Vein	12	4	0	5	3
16	Vein	5	3	1	1	0
17	Vein	5	0	3	1	1
18	Vein	11	6	0	2	3
19	Vein	11	1	3	1	6
Total		134	50 (76.9%)	15 (23.1%)	36 (52.2%)	33 (47.8%)

* Pneumonia.
† Anesthetic death.
‡ Anesthetic death?
§ Atelectasis.

and atelectasis, respectively, when injected, these conditions were undoubtedly important contributing factors in their deaths. If these two animals, and the one that suffered definitely an anesthetic death, are eliminated, there would be left only twelve that died when

injected during anesthesia. This would reduce to 18.5 per cent the number dying while under anesthesia, as opposed to 47.8 per cent dying when injected without anesthesia. None of the group dying without anesthesia showed any underlying pathological condition of the lungs at autopsy. All of the unanesthetized group that survived showed marked symptoms of anaphylaxis. None of the anesthetized group did. It is realized, of course, that the anesthetic may have masked some of the clinical signs of anaphyalaxis.

We believe that there is something unreliable in the results obtained in the group of animals injected intracardially. The heart of the guinea-pig is a relatively small and flimsy organ, and the ventricle is somewhat difficult to locate with the injecting needle. In some cases we had great difficulty in making the injections. We cannot help feeling that there is a mechanical factor which produces effects entirely aside from the effects of the injected serum. If we are correct in this supposition, the percentage of deaths in the animals injected while under anesthesia would be further reduced.

Two animals have been mentioned whose deaths were presumably due to anesthesia rather than the shocking injection. This factor is difficult to evaluate. The margin between the therapeutic and the toxic dose of ether is narrow in guinea-pigs. In order to see whether any deaths might result from ether alone, we anesthetized seventeen guinea-pigs, and kept them under the anesthetic for five minutes after surgical anesthesia had been induced. There were no deaths in this group. However, during the course of other experiments, on two occasions guinea-pigs that we had planned to inject with shocking doses while under anesthesia, died from the effects of the anesthetic before the injection could be made.

COMMENT

These experiments show that sensitized guinea-pigs subjected to shock-provoking injections, are much less likely to die in anaphylactic shock when the injections are made during ether anesthesia. Nevertheless, if these results are to be applied to man, the percentage of deaths is far too high to indicate that it is safe to inject foreign sera into human beings under the assumption that anesthesia will afford complete protection against anaphylaxis. It should be borne in

mind, however, that the guinea-pigs are more susceptible to anaphylactic shock, than are human beings, hence it is possible that any relative protection afforded by anesthesia may be more effective in the latter species.

CONCLUSIONS

(1) Ether narcosis in guinea-pigs definitely reduces the percentage of deaths from anaphylaxis, when animals sensitive to foreign protein are given shock-provoking injections during the period of narcosis.

(2) If the results obtained in guinea-pigs are transferrable to man, it is not a safe procedure to give tetanus antitoxin to patients while under ether anesthesia without preliminary skin or ophthalmic tests.

(3) We believe, although it has not been proven, that a patient known to be sensitive to horse serum, would be less likely to have a reaction if the serum were injected while he was under ether anesthesia. However, in such a case, if tetanus antitoxin must be given, we recommend testing the patient for sensitivity to some of the other sera in which the antitoxin is supplied, and, if the patient is not sensitive to one of these sera, we advocate its use instead of horse serum.[4]

[4] Dr. Franklin I. Harris of San Francisco, in duscussing this paper, made the following statement: "In reviewing the clinical work of surgery of hydatid disease written by Dr. Harold R. Dew of Melbourne, Australia, one finds an entire chapter devoted to the descriptive treatment and prevention of anaphylaxis produced by the rupture of a cyst and spilling of its contents into the peritoneal cavity. 'Owing to the abolition of the anaphylactic state by general anesthesia grave symptoms rarely, if ever, occur at operation even if much hydatid fluid is spilt into the wound. There is no doubt that operations on these cases under local anesthesia carry with them some risk of anaphylaxis and I have personally observed one patient operated upon by a colleague in whom a fatal result with all the symptoms of anaphylactic shock occurred.' This authority further points out that anaphylactic phenomena do occur if the effects of the general anesthesia have completely worn off so that in cases of hydatid disease the protection against this serious and common complication is transient and unquestionably due to the ether narcosis. He believes the delayed symptoms are due to the spilling of the fluid at the time of operation. So convinced are tropical surgeons of the protective action of ether narcosis that it has become an axiom that all operations even simple exploratory puncture with a needle in suspected hydatid disease should not be done under local anesthesia. Nevertheless I am in complete agreement with the statement that skin-tests should be routinely performed before the administration of antitoxin. It has been our practice to emphasize that the skin sensitivity test be done before ether anesthetic is administered because we believe that such anesthetic might mask an otherwise positive skin-test."

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A PRELIMINARY REPORT ON AN OPERATION FOR THE CURE OF MERALGIA PARAESTHETICA

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The purpose of this preliminary report is to present an operation which may supplant the present procedure of resecting the lateral femoral cutaneous nerve in cases of severe meralgia paraesthetica. Because a considerable amount of time usually elapses before a comprehensive report appears in print, and because in this interval of time cases may be lost to this new method of treatment, the present modification of the former operation is herewith described.

The original operation,[1] described in 1936, consisted simply of a complete neurolysis of the lateral femoral cutaneous nerve at the anterior inferior spine of the ilium. The patient operated on by this method was completely cured 8½ months after operation. The second patient, however, was only temporarily improved by the original method, and for him a modified osteoplastic procedure was devised. Now, more than 2 years after this operative intervention, he also is completely cured.

The new operation is performed as follows: An incision about 4 inches long is made transversely, slightly below the anterior superior spine of the ilium and almost parallel to the inguinal ligament. The lateral femoral cutaneous nerve is identified at the anterior inferior spine, and the external abdominal oblique aponeurosis and inguinal ligament are cut at their attachments near the anterior superior spine so that the nerve can be brought over the crest of the ilium. About one inch dorsal to the anterior superior spine a vertical groove about three-quarters of an inch long and one-quarter of an inch wide is cut in the bone so that the nerve can now rest without tension in its

[1] Lee, F. C. Meralgia paraesthetica. *International Clinics*, 1936, vol. 1, 46th series, p. 210.

new bed. One pedicle flap of fatty subcutaneous tissue is made to surround the nerve in its new groove of bone in order to prevent compression by subsequent bone growth. Another fat pedicle flap is applied to cover the nerve distal in its course from the ilium. The subcutaneous tissues and skin are then approximated.

A subsequent complete report will have illustrations of the operation and will show the sensory changes in the skin of the thigh after recovery has taken place. The results of these three operations indicate definitely that the cause of true meralgia paraesthetica is pressure and tension on the lateral femoral cutaneous nerve as it crosses the ilium, and that the cure for the condition is an osteoplastic neurolysis operation which relieves the nerve of these mechanical forces.

BOOK REVIEWS

(The reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Textbook of Nursing Practice. By HESTER K. FREDERICK AND ETHEL NORTHAM. 2nd ed., revised. 418 pp. Illus. $3.00. (*The Macmillan Company, New York, 1938.*)

In the second edition this book has been completely revised and amplified. The authors state that the space of the text does not permit a thorough discussion of the underlying principles of nursing. However, it is a most comprehensive handbook and contains invaluable detail. It should prove most helpful in all branches of nursing. The procedures described are those in vogue at the Johns Hopkins Hospital and, with certain variations, are accepted standard nursing procedures in most institutions. The illustrations are new and with few exceptions are adequate. More complete legends would have improved the illustrations, but the information can be obtained from the text itself. This book should prove to be most popular with the nursing profession at large.

W. B. A.

Insulin. Its Chemistry and Physiology. By HANS F. JENSEN. 252 pp. $2.00. (*The Commonwealth Fund. New York, 1938.*)

The chemistry of insulin has developed rapidly during the past twelve years; this advance being made possible by the isolation of crystalline insulin by J. J. Abel and his coworkers. Dr. Jensen, who was associated with Abel in many of the problems relating to the chemical properties of the crystalline protein, has reviewed in this book the facts gained not only from the chemical study of the molecule but also from the observations of its physiological activity.

Starting with a chapter on the historical background of the discovery of insulin, the author then discusses the preparation of insulin and the various methods used for purification, for crystallization and for standardization. Adequate reviews are also given of the effects by various reagents upon the activity of insulin, of modes of administration and of insulin substitutes. Finally there is a chapter dealing with the physiological action of insulin.

This book is to be recommended for its up-to-date and accurate summary of the major developments in the chemistry and physiology of insulin. Commendable are the many references with full titles given at the end of each chapter, the adequate author-and-subject index and the excellent printing and binding.

C. L. G.

Vitamin B_1 and its Use in Medicine. By ROBERT R. WILLIAMS, SC.D. AND TOM DOUGLAS SPIES, M.D. 411 pp. $5.00. (The Macmillan Medical Monographs.) (*The Macmillan Company, New York, 1938.*)

Deficiency of vitamin B_1 (thiamin) is the cause of beriberi, which, since the dawn of medical history has been one of the major health problems, as it is today, in populations subsisting largely upon polished rice. There is increasing evidence that deficiency of this nutrient occurs in the United States to a degree which impairs the health of a considerable number of people. It is, therefore, one of the most interesting of the food factors which are essential in the diet. Since its existence was first demonstrated by Eijkman, in 1897, thiamin has been the subject of many investigations. The greatest achievement in this field of research was the improvement of the yield of the vitamin by Dr. Williams from rice polishings, so that about an ounce of crystalline material was made available for chemical study. With this material, Dr. Williams and his associates succeeded in determining the structure of the molecule, and in following up this knowledge in an astonishingly short time by its synthesis. The synthetic vitamin has now become available at moderate cost in any quantities which may be necessary both for the prevention of beriberi and for clinical use.

In Part I of the book, the authors discuss in a concise way all aspects of thiamin deficiency which may be instructive to medically trained readers, and suggest the clinical conditions in which thiamin deficiency may be suspected. Every clinician should be familiar with the recorded experience with thiamin in therapy, and many, by reading this excellent discussion, will gain suggestions which may be applied in practice.

Part II is devoted to the fascinating story of the researches which have yielded our present knowledge of the vitamin, its physiological role, and its final synthesis.

This book should be read by every biochemist, physiologist and progressive physician. The reader may be assured that he will be entertained and instructed by it.

E. V. McC.

Diseases of the Skin. By GEORGE CLINTON ANDREWS. 2nd ed. reset. 899 pp. Illus. $10.00. (*W. B. Saunders Company, Philadelphia, 1938.*)

Dr. Andrews's book, already one of our leading texts, has been made more attractive in the second edition. The chapters on several diseases have been rewritten completely, and some seventy-five new affections have been recorded. The photographs are numerous and excellent, I have never seen a better collection. The subject matter is relatively short, and the author is to be congratulated for leaving out a lot of useless prescriptions which in many books are merely rearrangements, in a little different proportion, of the old ones. Pathology is in most cases adequately discussed. All together the book may be very highly recommended for both student and general physician.

L. W. K.

A General Textbook of Nursing. A Comprehensive Guide. By EVELYN C. PEARCE. 888 pp. Illus. $3.75. (*E. P. Dutton & Co., New York, 1938.*)

This book is indeed a comprehensive one, as stated in the title, for it covers a wide field in nursing. It considers the general care of the patient and deals with the simple fundamental nursing procedures as well as the special measures required in the more serious types of illness. It takes up the subjects of feeding the patient and of elementary dietetics, the administration of medicines, and the nursing care and treatment of medical patients in a wide range of conditions including the infectious diseases. Gynaecological nursing is considered, with the special techniques utilized in this field. A brief explanation of the prenatal and postnatal care of obstetric patients is given. The book concludes with a description of general surgical nursing and its branches of allied specialties. Throughout the book emphasis is placed on the necessity for consideration by the nurse of the patient's mental attitude. The treatments and procedures as they are described, are made clearer by many excellent photographs.

The author has had an extensive experience as a nurse, as an instructor in English schools of nursing and as a writer of a number of textbooks for nurses. This book has been written as a guide for undergraduate nurses during the course in the nursing school of the hospital, and as an aid in preparing nurses for their future responsibilities.

The book follows the English plan of teaching in schools of nursing, which differs somewhat from the methods used in this country. The extent of the information covered does not allow space for general discussion of the material presented but the subject matter is treated in a concise and interesting manner. Any nurse engaged in the active practice of nursing will find the book useful as a reference, and helpful in bringing to her attention the newer forms of treatment resulting from scientific developments in the field of medicine.

H. K. F.

Enfermedades por infección de las amigdalas. By RAFAEL ROMERO RODRIGUEZ. 165 pp. Unbound, 7 pesetas. Imprenta de la Divina Pastora, Seville, 1935.

In this monograph of 157 pages the author presents his personal methods for the diagnosis of tonsillar infection, his ideas concerning the significance of these infections as a basis for certain disease processes and his method for tonsillectomy. He has gone extensively into the question of indications for surgery and although he has very little if anything new to add to our conception of the importance of foci of infection he has made a workmanlike effort.

L. M.

Physiology of Anesthesia. By HENRY K. BEECHER. 402 pp. $3.75. Oxford University Press, New York, 1938. (Oxford Medical Publications.)

The material presented in this volume was originially used for teaching purposes at the Harvard Medical School. The purpose of the book is to describe

the response of the body to anesthetic agents, in other words, to discuss the pharmacology of anesthetics. The book consists of four chapters on 1) effects of anesthesia on the nervous system, 2) the respiration and anesthesia, 3) the circulation and anesthesia, and 4) organic effects of anesthetic agents. It is distinctly not a manual of the art of anesthesia for anesthetists, but is an attempt to consider the fundamental principles underlying the use of anesthetics.

The material is presented in readable form, is accurate, and takes cognizance of recent work. A good bibliography is appended. The volume should prove of interests to medical students and professional anesthetists.

E. K. M., Jr.

Medicine in the Outpatient Department. By Winthrop Wetherbee, Jr. 111 pp. $1.00. Paul B. Hoeber, New York, 1938.

This little book by one of the Junior Physicians of the Boston City Hospital, sponsored by George R. Minot, is put out in inexpensive form. It is intended for use by the medical student at the time he comes into contact with patients in the Outpatient Department.

There are certain general considerations in regard to the technique and attitude of the student that are helpful. Among these is a good set of directions for history taking, in which the present illness is described first. For use in clinics in which it is customary to record the family history, past history, and present illness in the order named, this scheme will have to be reversed. The book also contains some valuable "clinical maxims." The weakness in listing such maxims is one of extent rather than of quality; for, while the aphorisms contained in this small volume are very good precepts in the practice of medicine, medicine is so broad that the list hardly scratches the surface. Nevertheless, it is to be recommended as valuable reading for any student, especially during the second and third years of his medical career.

J. T. K.

Carbon Monoxide Asphyxia. By Cecil K. Drinker. 276 pp. Illus. $4.50. Oxford University Press. New York. 1938 (Oxford Medical Publications).

Although this book was written primarily for industrial workers, much of the material is of interest to physiologists and to biochemists for it describes an important application of the modern advances in physiology and biochemistry to an industrial problem.

The context of the book contains an elementary but adequate description of the gaseous exchange in the lungs and of the transport of oxygen and of carbon monoxide by the blood. Following this, there is an excellent account of the physiological and anatomical changes induced in the body by acute and chronic carbon monoxide poisoning and a discussion of the treatment of these conditions. In the final chapter, written by Dr. Sendroy, the methods devised for the estimation of carbon monoxide are reviewed in detail. The authors give numerous

references to the work done in each field and have critically evaluated the evidence obtained from many sources.

This book fulfills its purpose and is to be recommended to everyone interested either in the theoretical or the practical aspects of carbon monoxide poisoning.

C. L. G.

Materia Medica, Drug Administration and Prescription Writing. By OSCAR W. BETHEA. 5th revised ed. 577 pp. $5.00. F. A. Davis Company, Philadelphia, 1938.

The fifth edition of Bethea's Materia Medica has been extensively revised, in conformity with the U. S. Pharmacopoeia XI. The official preparations are described in the usual way, and their uses and methods of administration are briefly but adequately discussed. A very useful feature is the inclusion of a large number of prescriptions illustrating the use of practically every drug commonly employed. Preparations in *New & Non-official Remedies* are not considered.

In Part II the technique of prescription writing is considered in detail, the chief difficulties are discussed, and some common errors are illustrated.

The book should prove valuable both as a text book for students and as a reference book.

P. W. C.

BOOKS RECEIVED FOR REVIEW

Diseases of the Chest and the Principles of Physical Diagnosis. By GEORGE W. NORRIS and H. R. M. LANDIS. 6th ed. revised. 1019 pp. Illus. $10.00. *W. B. Saunders Company, Philadelphia, 1938.*

The Pneumonias. By HOBART A. REIMANN. 381 pp. Illus. $5.50. *W. B. Saunders Company, Philadelphia, 1938.*

Plastic Surgery. By ARTHUR JOSEPH BARSKY. 355 pp. Illus. $5.75. *W. B. Saunders Company, Philadelphia, 1938.*

Etiology of Trachoma. By LOUIS A. JULIANELLE. 248 pp. Illus. $3.25. *The Commonwealth Fund, New York, 1938.*

Technique of Contraception. By ERIC M. MATSNER. 4th ed. 50 pp. Paper bound. *National Medical Council on Birth Control, New York, 1938.*

Die Ernährung der olympischen Kämpfer in Vergangenheit und Gegenwart. By ADOLF BICKEL. 36 pp. Illus. Paper bound, R.M. 1.00. *Deutsche Verlagsgesellschaft m. b. H., Berlin, 1938.*

British Periodicals of Medicine. A Chronological List. By W. R. LEFANU. 93 pp. $1.25. *The Johns Hopkins Press, Baltimore, 1938.* [Reprinted from *Bulletin of the Institute of the History of Medicine*, Vol. V, Nos. 8 and 9, October and November, 1937 and Vol. VI, No. 6, June, 1938.]

The New-born Infant. A Manual of Obstetrical Pediatrics. By EMERSON L. STONE. 2nd ed. revised. 291 pp. $3.00. *Lea & Febiger, Philadelphia, 1938.*

Principles and Practice of Obstetrics. By JOSEPH B. DELEE. 7th ed. 1211 pp. Illus. $12.00. *W. B. Saunders Company, Philadelphia, 1938.*

Human Pathology. By HOWARD T. KARSNER. 5th ed. revised. 1013 pp. Illus. $10.00. *J. B. Lippincott Company, Philadelphia, 1938.*

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Pediatric Nursing. By M. CORINNE BANCROFT, ELIZABETH PIERCE and BESSIE CUTLER. 3rd ed. 652 pp. Illus. $3.00. *The Macmillan Company, New York, 1938.*

Social Hygiene Nursing Techniques. By NADINE B. GEITZ. 82 pp. 25 cents. *American Social Hygiene Association, New York, 1938.*

The Practice of Medicine. By JONATHAN CAMPBELL MEAKINS. 2nd ed. 1413 pp. Illus. $12.50. *C. V. Mosby Company, St. Louis, 1938.*

Explorations in Personality. By HENRY A. MURRAY. 761 pp. $8.50. *Oxford University Press, New York, 1938.*

Jacob Henle: on Miasmata and Contagia. Translated by GEORGE ROSEN. 77 pp. $1.00. *The Johns Hopkins Press, Baltimore, 1938.*